ARCHIVES of INTERNAL MEDICINE

VOLUME 73 APRIL 1944 NUMBER 4

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DERMATOMYOSITIS

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Dermatomyositis is frequently unrecognized because of lack of familiarity with its variable clinical manifestations. In the advanced stage of the illness the diagnosis is seldom difficult. This report concerns the clinical and laboratory findings and biopsy observations on muscle in the cases of 9 patients with dermatomyositis who were observed in Vanderbilt Hospital during one year. A certain number of the cases in this series were atypical, yet there were sufficient significant features to justify this diagnosis.

The cause of dermatomyositis is unknown. Frequently the earliest symptom is preceded by an acute infection. Although this disease may occur at any age, it usually occurs between the ages of 10 and 50 years. There is no significant sex predominance. Pathologically the salient lesions are present in the striated muscles; however, many other structures may be implicated. The onset of the disease may be abrupt or insidious; remissions and exacerbations are frequent. The course of the illness varies from weeks to years. The outcome is reported to be fatal in 50 to 60 per cent of the cases.

The most characteristic feature of this disease is the involvement of muscles, which often produces the earliest symptoms. Muscular pains, tenderness, stiffness and fatigue are common complaints and may be localized or generalized at the onset of the illness. As the disease progresses, the muscles of the shoulder and of the pelvic girdle as well as the proximal muscles of the extremities are affected in particular. The consistence of the involved muscles is variable. Late in the illness atrophy and contractures of the muscles may occur. The extrinsic orbital muscles, the muscles of the jaw, tongue, pharynx and larynx, the intercostal muscles and the diaphragm may be affected. Involvement of the diaphragms with subsequent respiratory paralysis or pulmonary infection is the most common cause of death. There is both clinical and anatomic evidence to show that the heart may be involved, although this is not common.[1] Rarely death may result from cardiac failure.

Cutaneous lesions usually develop during the illness. While ordinarily erythematous, the eruption is nonspecific and may simulate a variety of dermatologic conditions.[2] Other cutaneous manifestations include hyperhidrosis, loss of hair, pigmentation, telangiectases, sclerodermatous changes and subcutaneous calcification. There may be lesions of the mucous membranes.[3] Brawny or soft edema, often accompanied by erythema, is a frequent finding. Vasomotor disturbances, particularly Raynaud phenomena, are present in many instances and may constitute the earliest symptoms.

Headache, fever, easy fatigability and loss of weight are common complaints. There may be paresthesias or muscular cramps. Hemorrhagic manifestations, with purpura, epistaxes and bleeding into the intestine and kidneys, have been observed.[4] There may be arthritic pains, although these usually have been ascribed to

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1. (*a*) O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of Forty Cases, Arch. Dermat. & Syph. **41**:1001-1019 (June) 1940. (*b*) Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. f. Dermat. u. Syph. **178**:414-468, 1939. (*c*) Kinney, T. D., and Maher, M. M.: Dermatomyositis: A Study of Five Cases, Am. J. Path. **16**:561-594 (Sept.) 1940. (*d*) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: II. A Comparative Study of the Essential Clinicopathologic Features, Arch. Int. Med. **66**:339-383 (Aug.) 1940.

2. (*a*) Keller, R.: Zur Dermatomyositis im Kindesalter, Ztschr. f. Kinderh. **58**:551-563, 1936. (*b*) Karelitz, S., and Welt, S. K.: Dermatomyositis, Am. J. Dis. Child. **43**:1134-1149 (May) 1932. (*c*) Keil, H.: The Manifestations in the Skin and Mucous Membranes in Dermatomyositis with Special Reference to the Differential Diagnosis from Systemic Lupus Erthematosus, Ann. Int. Med. **16**:828-871 (May) 1942.

3. O'Leary and Waisman.[1a] Schuermann.[1b] Keil.[2c]

4. (*a*) Schuermann.[1b] (*b*) Marcus, I. H., and Weinstein, J.: Dermatomyositis: A Report of a Case with a Review of the Literature, Ann. Int. Med. **9**:406-425 (Oct.) 1935. (*c*) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: I. A Clinical Report of "Transitional" Cases with a Consideration of Lead as a Possible Etiologic Factor, Arch. Int. Med. **66**:109-139 (July) 1940.

tendinous and periarticular involvement rather than to actual disease of joints.[5] Additional findings have included retinal changes,[6] splenomegaly and hepatomegaly, enlargement of lymph nodes,[7] effusions into body cavities[1b] and decreased tendon reflexes.[8] The laboratory and pathologic aspects of this disease will be mentioned later.

The diagnosis of dermatomyositis depends on clinical and pathologic observations. In the differential diagnosis, most difficulty arises in distinguishing dermatomyositis from scleroderma. Much clinical and pathologic evidence has been presented to show that these two conditions are merely variations of a single disorder.[9] Certain observers, however, contend that they are clinically and pathologically distinct.[10] Disseminated lupus erythematosus, periarteritis nodosa, early rheumatic fever, early rheumatoid arthritis, trichiniasis, polyneuritis and epidemic myalgia are only a few of the conditions which may be confused with dermatomyositis.

Treatment of dermatomyositis has been unsatisfactory. In many instances salicylates do not relieve the muscular symptoms.[11] Milhorat and his co-workers[12] noted some clinical improvement after administration of vitamin E. Other therapeutic measures have included rest, physical therapy, administration of potassium iodide, transfusions, administration of vitamins, treatment with neoarsphenamine and inhalations of oxygen.

5. O'Leary and Waisman.[1a] Keil.[1d] Marcus and Weinstein.[4b]

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9. (*a*) Freudenthal, W.: Generalized Scleroderma and Dermatomyositis: A Histological Comparison, Brit. J. Dermat. **52**:289-295 (Oct.) 1940. (*b*) Lewis, T.: Notes on Scleroderma (Dermatomyositis), ibid. **52**: 233-242 (Aug.-Sept.) 1940. (*c*) Dowling, G. B.: Generalized Sclerodermia, ibid. **52**:242-256 (Aug.-Sept.) 1940. (*d*) Hecht, M. S.: Dermatomyositis in Childhood, J. Pediat. **17**:791-800 (Dec.) 1940.

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11. Schuermann.[1b] Holler.[7a]

12. Milhorat, A. T.; Weber, F. C., and Toscani, V.: Metabolic Studies in Dermatomyositis with a Note on the Effect of Wheat Germ, Proc. Soc. Exper. Biol. & Med. **43**:470-473 (March) 1940.

REPORT OF CASES

CASE 1.—H. H., a 59 year old white farmer, was well until eight years prior to admission to the hospital, when there was a gradual onset of generalized weakness, stiffness and soreness of the muscles. Soon afterward there appeared dyspnea on exertion, anorexia and slight dysphagia. During the prolonged illness his weight fell from 220 to 120 pounds (99 to 54 Kg.). Four years before admission the patient began to have recurrent attacks of symmetric discoloration and pain of the fingers, hands and lower part of the forearms after exposure to cold air. One year later, after a severe attack of "influenza," a chronic productive cough developed. In the four year period prior to admission to the hospital the patient was followed irregularly in the outpatient clinic, where it was felt that the majority of his complaints were psychogenic. In March 1939 he was found to have a scaly papular

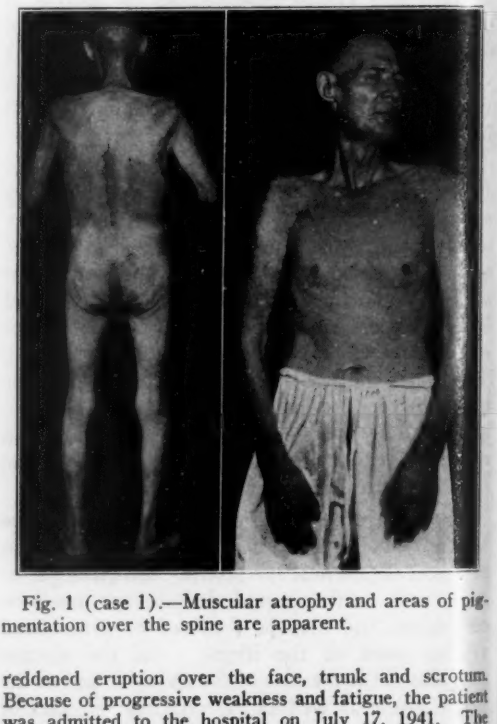

Fig. 1 (case 1).—Muscular atrophy and areas of pigmentation over the spine are apparent.

reddened eruption over the face, trunk and scrotum. Because of progressive weakness and fatigue, the patient was admitted to the hospital on July 17, 1941. The past history and family history were not contributory.

Physical Examination.—This revealed an emaciated white man. The skin of the face and of the distal portions of the extremities was thickened and adherent to underlying structures. Over the lower part of the lumbar region of the spine and the gluteal region the skin was thickened and exhibited a bluish brown discoloration. The scrotum showed splotchy brown pigmented areas. Numerous telangiectases were present on the face. Muscular atrophy, while generalized, was most striking in the sternomastoid muscles and the muscles of the shoulder and pelvic girdles. The musculature of the proximal portions of the extremities was more atrophic than that of the distal portions. The muscles were flabby and presented diffuse moderate tenderness. The chest was emphysematous. Moist rales

were present at the base of each lung. The heart was within normal limits. The blood pressure was not elevated. The liver was slightly enlarged. There were cyanosis and early clubbing of the nail beds. Slight brawny pitting edema was present over the ankles.

Laboratory Studies.—There was no anemia. The total leukocyte count was 10,600 per cubic millimeter, with a differential count of 71 per cent neutrophils, 6 per cent eosinophils, 17 per cent lymphocytes and 6 per cent monocytes. Examinations of the urine and stools showed them to be normal. The total serum protein amounted to 8 Gm. per hundred cubic centimeters, with albumin 3.7 Gm. and globulin 4.3 Gm. . Roentgenograms of the sinuses, chest and long bones showed no abnormality. Fluoroscopic examination of the chest showed diminished excursion of the diaphragm and poor expansion of the thoracic cage. An electrocardiogram showed deviation of the axis to the right with a normal sinus rhythm. The basal metabolic rate was + 3 per cent.

Biopsy.—A section of skin showed atrophy of the epidermis and slight perivascular lymphocytic infiltration of the corium. A biopsy of the gastrocnemius muscle showed: a pronounced focal increase in the muscle nuclei; degenerating muscle fibers, some of which were undergoing phagocytosis; focal increase in interstitial tissue; moderate infiltration of inflammatory cells into the interstitial substance; occasional multinucleated cells, and focal collections of brown pigment granules in the interstitial connective tissue.

Course in the Hospital.—The patient was observed for fifteen days. During this time the temperature and pulse remained normal. Therapy consisted of frequent warm baths and oral administration of potassium iodide, acetylsalicylic acid and 40 mg. of alpha tocopherol daily. The vital capacity was slightly reduced. The venous pressure and the circulation time were normal. The patient was digitalized, without improvement. At the time of his discharge his condition was unchanged.

One month later he reentered the hospital for a period of six weeks. Because of anorexia, increased weakness and persistent abdominal fulness, he had remained in bed during the intervening period. On examination there was little change except for severe bradycardia and an irregular cardiac rhythm. An electrocardiogram showed auricular fibrillation. Digitalis was omitted. Quinidine was given, and after a short period of regular rhythm auricular flutter with varying degrees of heart block supervened and persisted. The venous pressure was now slightly elevated, measuring 130 mm. of saline solution, and the circulation time (determined with paraldehyde and sodium cyanide) was prolonged. The vital capacity was unchanged. The total serum protein was now 10.42 Gm. per hundred cubic centimeters, with albumin 4.85 Gm. and globulin 5.57 Gm. Tests of hepatic function showed no impairment. Roentgenograms of the gastrointestinal tract were normal.

The patient remained afebrile throughout this period. After administration of digitalis was discontinued the pulse rate became normal. The muscular complaints persisted, and dyspnea was a prominent feature. There was little symptomatic improvement.

For several months following discharge the patient continued to take alpha tocopherol without benefit. Six months later he appeared slightly improved. He had gained 15 pounds (6.75 Kg.) in weight. He still complained of severe dyspnea and a productive cough. For four months he had been taking large amounts of vitamin concentrates. The development of telangiectases on the palmar aspects of the hands was noted. An electrocardiogram still showed deviation of the axis to the right and auricular flutter with variable block.

CASE 2.—W. B., a 56 year old white carpenter, entered the hospital on Oct. 27, 1941. Since 1928 the patient had been followed in the outpatient clinic of this hospital for numerous complaints, and various diagnoses had included chronic sinusitis, chronic bronchitis, emphysema and arteriosclerotic heart disease. The earliest complaint referable to the present illness occurred in February 1941, when there was intermittent periorbital edema for several weeks. In March 1941 the patient had "influenza" with chills, fever, malaise and a sore throat, accompanied by generalized pains and stiffness of the muscles. The chronic cough which had been present for years became more severe and productive of as much as 16 ounces (480 cc.) of sputum daily. The acute febrile illness was of short duration. The muscular stiffness and soreness persisted, especially in the lower part of the back, legs and shoulders. He began to have cramps in the muscles, particularly at night, and also noticed occasional coarse twitching of the muscles. There was progressive loss of strength and of muscle substance, mainly in the buttocks and trunk. In May 1941 he first noted that after exposure to cold his hands became blue and painful. Shortly afterward he noted that cuts on the face and hands bled less profusely than formerly. This was followed by intermittent hoarseness, occasional double vision and difficulty in swallowing with occasional regurgitation of solid food. Dyspnea was

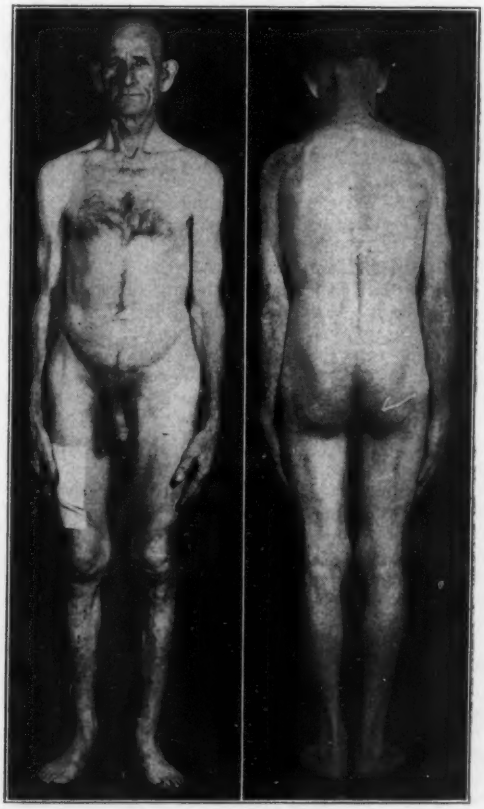

Fig. 2 (case 2).—Muscular atrophy and pigmentation are present.

more severe with the present illness. There was an intermittent low grade fever. The weight fell from 156 to 126 pounds (70 to 57 Kg.) in the year prior to admission.

Physical Examination.—The patient was a poorly developed, emaciated man. There was no abnormality of the head and neck. The chest was emphysematous, with a low diaphragm. The lungs were clear. The heart was normal, and the blood pressure was not elevated. The peripheral vessels were sclerotic. The edge of the liver was palpable 4 cm. below the costal margin. The spleen could not be felt. The skin was not thickened, and there was no rash. Although there was generalized muscular atrophy, this was most marked in the pelvic and shoulder girdles, calves and thighs. Weakness was more pronounced in the proximal portions of the extremities. There was tenderness in the pectoral muscles, the trapezius muscles and the calf muscles.

Laboratory Studies.—There was no anemia. The total leukocyte count was not elevated, varying between 5,900 and 7,900 per cubic millimeter. The differential count showed 67 per cent neutrophils, 25 per cent lymphocytes and 8 per cent monocytes. The sedimentation rate was not elevated. Examinations of the stools and urine revealed nothing abnormal. The total serum protein was 7.3 Gm. per hundred cubic centimeters, with albumin 5.01 Gm. and globulin 2.30 Gm. The hippuric acid and bromsulphalein tests of hepatic function showed no impairment. Roentgenograms of the chest showed increased bronchovascular shadows at the bases of the lungs, and roentgenograms of the sinuses showed no abnormality. Bronchograms were normal. An electrocardiogram was normal. The basal metabolic rate was + 1 per cent.

Biopsy of the Quadriceps Muscle and Overlying Skin.—The skin showed atrophy of the epidermis and moderate lymphocytic infiltration into the perivascular connective tissue of the corium. The muscle showed a great increase in nuclei, degenerating muscle fibers undergoing phagocytosis and slight focal increase in connective tissue, which was infiltrated with moderate numbers of lymphocytes and histiocytes. The inflammatory reaction was most pronounced about the vessels.

Course in the Hospital.—The first admission was for seventeen days. During this time the temperature and pulse rate were not elevated. No specific treatment was employed. Postural drainage was without effect. The patient was discharged Nov. 13, 1941, without evident improvement.

After his discharge the productive cough continued and dyspnea increased. He noted progressive weakness of the forearms and hands, and the muscular stiffness, cramps and twitching persisted to such a degree that he was unable to work.

On Feb. 23, 1942 he reentered the hospital for a period of ten days. There were no additional significant physical findings. The vital capacity was reduced, being 2.6 liters. The circulation times (measured with paraldehyde and sodium cyanide) were slightly prolonged, although there was no elevation of the venous pressure. Fluoroscopic examination of the chest showed poor excursion of the diaphragm and increased excursion of the thoracic cage. The patient did not improve. There was no fever. Oral administration of alpha tocopherol (40 mg. daily) and of acetylsalicylic acid was instituted and continued after discharge from the hospital.

On April 18, six weeks after the second discharge, the patient reentered the hospital. The muscular symptoms, weakness and productive cough had persisted. There was frequent periorbital edema, and difficulty in swallowing was greater. Three days prior to his admission respiratory distress became acute and obliged the patient to remain in bed. Pains in the muscles became severe. The patient now appeared severely dyspneic and cyanotic. Breathing was effected entirely by the accessory muscles of respiration. Small punctate erythematous lesions were present on the palate. There was a light brown scaly exfoliation of skin of the anterior abdominal wall. Muscular tenderness was generalized. The lungs were clear, and the heart was normal.

The patient was placed in an oxygen tent, where he remained for five days. During this period there were daily rises of temperature to 102 F. A roentgenogram of the chest showed the lungs to be clear. With the fever there was no leukocytosis, although the sedimentation rate was rapid. Several injections of neostigmine methylsulfate administered soon after his admission had no appreciable effect on the respiratory paralysis. The patient slowly improved and was discharged thirteen days after admission. By this time the respiratory difficulty had diminished.

CASE 3.—L. D., a 65 year old white man, entered the hospital on Nov. 25, 1940. For two years he had experienced dyspnea on exertion and increasing fatigability. In May 1939 an erythematous rash had appeared on his face. This was treated with roentgen therapy, after which it slowly disappeared. At the same time he began to have periorbital edema, particularly in the mornings. In November 1939 redness and swelling of the hands occurred, and these persisted. In September 1940 redness of the skin of the elbows was noted. For one year prior to admission the patient had had a chronic productive cough.

Physical Examination.—The patient was well developed and well nourished. The skin of the face was thickened and reddened. Pitting edema of the face was present. Numerous telangiectases were present on the face, scalp, thorax and soft palate. The hands and wrists were swollen, with thickening and redness of the overlying skin. The chest was emphysematous. Rales were heard at the bases of the lungs. The heart was normal. The blood pressure was not elevated. The edge of the liver was felt 4 cm. below the costal margin, and the spleen was not palpable. No tenderness or atrophy of muscles was observed.

Laboratory Studies.—There was a slight normochromic, normocytic anemia, with hemoglobin 12.2 Gm. per hundred cubic centimeters. The total leukocyte count was 5,000 per cubic millimeter, with a differential count of 59 per cent neutrophils, 14 per cent lymphocytes, 26 per cent monocytes and 1 per cent eosinophils. The corrected sedimentation rate was not elevated. Examinations of urine and stools showed them to be normal. Roentgenograms of the long bones, spine, skull and chest were normal. The plasma protein was normal. Tests of renal and of hepatic function gave normal results.

Biopsy of Skin and Muscle.—A section of skin showed slight perivascular lymphocytic infiltration of the corium. A section of muscle showed degenerative and proliferative changes of the fibers, with slight increase in interstitial tissue, occasional giant cells and focal interstitial collections of lymphocytes and histiocytes.

Course in the Hospital.—During the seven day period of observation the temperature showed frequent rises to 99.6 F. (oral). The patient was treated with parenteral injections of liver extract. There was no

clinical improvement, and no definite diagnosis was made.

Subsequently there developed persistent stiffness and pain in the muscles, which were made worse by exercise. Chronic hoarseness appeared. Paresthesias occurred in the hands and feet. The swelling of the face and hands subsided after six months. Trophic ulcerations appeared on the knuckles. No Raynaud phenomena were observed. More telangiectases appeared on the skin. The weakness, dyspnea and chronic cough continued; however, the patient was subjectively improved after prolonged vacation.

On Nov. 6, 1941, one year after the original admission, the patient returned for examination. He had lost 5 pounds (2.25 Kg.) in weight during the year. The skin of the hands and the lower part of the forearms was rough and thickened, with a brownish red discoloration. A healing ulcer was present over an interphalangeal joint. The skin of the feet was erythematous and cool. There was no edema. The telangiectases, originally noted, persisted. Rales were present at the base of each lung posteriorly. The liver and spleen were not palpable. There were atrophy and weakness of the musculature of the shoulder girdle. No muscular tenderness was demonstrable.

The hemoglobin content and the total erythrocyte count were unchanged. The total leukocyte count was 5,200 per cubic millimeter, with a differential count of 60 per cent neutrophils, 20 per cent lymphocytes, 15 per cent monocytes and 5 per cent eosinophils. The corrected sedimentation rate was moderately elevated. An electrocardiogram was normal.

Case 4.—M. B., a 35 year old white woman, a nurse, was seen in the hospital Jan. 20, 1942. In September 1938, following extraction of a tooth, an abscess developed in the left side of the upper jaw; this continued to drain for three months. During this time she began to experience pains in the calves of her legs. In January 1940 painful, indurated vesicular lesions appeared on the fingers and dorsal aspects of the hands; these persisted for several months. There were repeated paronychias. The rash on the hands was followed by a painful red discoloration of the neck, which remained for three months and left a residual light brown pigmentation. In August 1941 the extensor surfaces of the thighs were covered with a painful erythematous rash, which persisted for several months. This was followed by a symmetric erythema of the face and a scarlatiniform eruption involving the shoulders, axillary folds and elbows. This rash disappeared after several months, leaving a residual brownish discoloration and flaky desquamation.

For one year prior to examination the patient's face had been swollen, particularly in the mornings. For six months she had observed that her hands and forearms became blue and painful following exposure to cold. Intermittent painless swelling of the hands occurred. A feeling of numbness was frequently present in the extremities. There was dyspnea on exertion. For two months there were severe pain, tenderness and stiffness of the muscles of the arms and shoulder girdle. There were frequent nocturnal cramps of the quadriceps muscles, and fibrillary twitchings were noted in the muscles of the right thigh. Recently the patient had become aware of thickening of the skin of the face and increased axillary sweating. The appetite had remained good, and there had been no loss of weight. For six weeks the patient had been taking large amounts of alpha tocopherol by mouth, without benefit except for a decrease in the numbness of the hands and feet.

The past history included an attack of pyelitis in 1935. In September 1939 the patient had a spontaneous abortion of six weeks. In September 1940 an eight month pregnancy terminated in a stillbirth. During the past year the menstrual flow had diminished in amount.

Physical Examination.—The patient was well developed and well nourished. There was light brown pigmentation of the skin of the cheeks, neck and anterior axillary folds. The fingers showed fusiform swelling, and the overlying skin was shiny and atrophic and in places was adherent to underlying tissues. There was a blotchy red discoloration of the hands, with focal areas of depigmentation. A single trophic ulcer was present. There was moderate periorbital edema. The isthmus and the right lobe of the thyroid were diffusely enlarged. The heart and lungs appeared normal. Tenderness was marked in the muscles of the arms and was less severe in the muscles of the shoulder girdle and forearm. There was no muscular atrophy.

Laboratory Studies.—There was no anemia. The total leukocyte count was 5,400 per cubic millimeter, with 46 per cent neutrophils, 46 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The sedimentation rate was not elevated. The urine was normal. An electrocardiogram was within normal limits. Fluoroscopic examination of the chest showed good excursion of the diaphragm. The total serum protein was 7.19 Gm. per hundred cubic centimeters, with albumin 4.33 Gm. and globulin 2.86 Gm. The basal metabolic rate was normal (—8 and 5 per cent).

Case 5.—J. J., a 51 year old white farmer, entered the hospital on Oct. 6, 1941. Eight months previously he had a "cold" characterized by a sore throat, nasal discharge and vague muscular pains. Ten days later his face, hands and ankles became swollen. The swelling continued for six weeks and thereafter recurred intermittently. Several months later he noticed pain and stiffness of the muscles of the extremities. These were most severe in the mornings and were relieved by gentle exercise but aggravated by moderate or severe exertion. One month before admission to the hospital he first noticed thickening and pigmentation of the skin of the extremities and later of the entire body. There were a progressive loss of strength and a loss of 27 pounds (12 Kg.) of weight during the present illness. No Raynaud phenomena were noted.

Physical Examination.—The patient was poorly nourished and appeared chronically ill. There was a uniform dusky brown pigmentation of the skin except for an area of bluish brown discoloration over the thoracic and lumbar regions of the spine. There were splotchy areas of depigmentation of the face, forearms and hands. The skin of the entire body was thickened and adherent to underlying structures. Thickening was most pronounced in the face, distal portions of the extremities and scrotum. There was moderate diffuse muscular atrophy but no demonstrable muscular tenderness. Because of the thickened skin, motion of the fingers, wrists, elbows, ankles and knees was limited. The remainder of the examination failed to show anything abnormal.

Laboratory Studies.—There was no anemia. The total leukocyte count was 16,600 per cubic millimeter, and subsequent determinations showed little change. Differential counts showed an increase in neutrophils without any increase in monocytes or eosinophils. The sedimentation rate of the blood was persistently elevated. Examinations of the urine and stools gave normal results. Roentgenograms of the hands and

feet showed no abnormality, while one of the chest showed apical fibrosis. The serum cholesterol (during fasting) was 161 mg. per hundred cubic centimeters. The serum protein and the albumin and globulin were normal. The basal metabolic rate was moderately elevated on three occasions (+25, +15 and +11 per cent).

Biopsy of the Quadriceps Muscle and Overlying Skin.—The skin showed extreme thickening and hyalinization of the corium, with perivascular lymphocytic infiltration. The muscle showed a moderate increase in the number of nuclei and slight infiltration of the interstitial tissue with lymphocytes and histiocytes. A few necrotic muscle fibers appeared to be undergoing phagocytosis.

Course in the Hospital.—The patient was observed for three weeks. The temperature was frequently elevated to 100 F. (oral), and the pulse rate varied between 70 and 100. Various therapeutic procedures

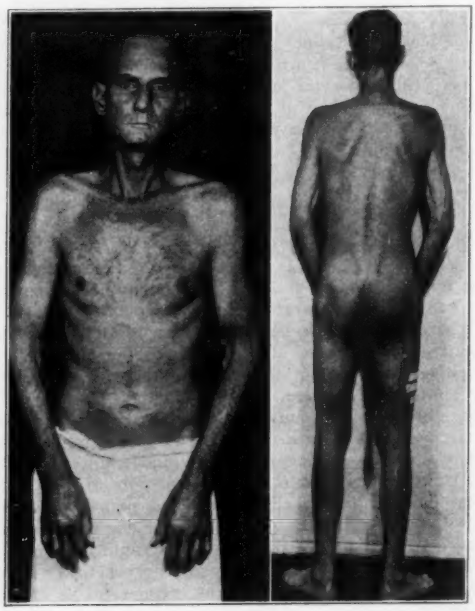

Fig. 3 (case 5).—Pigmentation may be seen over the spine.

were employed. Warm baths and fever therapy with typhoid vaccine were ineffective. Local application of methyl salicylate gave no relief. An attempt to produce cutaneous vasodilatation with intravenous administration of a saline solution containing 3 mg. of histamine gave no response. Likewise 1 Gm. of nicotinic acid given intravenously had no effect on the cutaneous temperature. There was no clinical improvement. At the time of discharge the patient was instructed to take 4 Gm. of potassium iodide daily. One month later his status was unchanged.

CASE 6.—R. W., a 52 year old white man, entered the hospital on March 29, 1942, complaining of dyspnea and muscular pains. Five years previously he had an episode of severe substernal pain which persisted for five hours. He was told then that he had hypertension. Thereafter he had dyspnea on exertion, paroxysmal nocturnal dyspnea, a chronic productive cough and occasional precordial pain. In 1940 he had an operation for a strangulated abdominal hernia, and several months later, an operation for an inguinal hernia. After the second operation and approximately eighteen months prior to his admission to the hospital, there was a gradual onset of muscular pains and stiffness, which were more severe in the arms than in the legs. Simultaneously, a blotchy erythematous eruption appeared on the trunk. This rash never caused any discomfort and disappeared and recurred intermittently during the next eighteen months. The muscular stiffness and soreness persisted in the extremities and were relieved slightly by acetylsalicylic acid. There were occasional paresthesias in the lower extremities and frequent nocturnal cramps in the muscles of the legs. For at least one year there had been periorbital edema, particularly in the morning. Hoarseness was a troublesome symptom during the present illness. There was no loss of weight.

Physical Examination.—The patient was an obese, dyspneic elderly man. He had slight cyanosis of the nail beds. The retinal arteries showed sclerotic changes. The chest was emphysematous. There were numerous moist rales over the lower portion of each lung posteriorly. The heart was slightly enlarged and had a regular rhythm. The blood pressure was 150 systolic and 105 diastolic. The liver and spleen were not enlarged. There was no edema. Tenderness to deep pressure was elicited over the trapezius muscles and the muscles of the upper parts of the arms, thighs and calves. There was no atrophy of muscles. Neurologic examination gave negative results. Over the thorax there were several pink maculopapular lesions which measured 3 cm. in diameter. One similar lesion was present on the right elbow.

Laboratory Studies.—The hemoglobin content was 10 Gm. per hundred cubic centimeters. The erythrocyte count was 3,000,000 per cubic millimeter, and the total leukocyte count, 8,700, with a normal differential count. The corrected sedimentation rate was elevated. The urine was normal. The total serum protein amounted to 9.70 Gm. per hundred cubic centimeters, with albumin 2.91 Gm. and globulin of 6.79 Gm. The basal metabolic rate was +17 per cent. A roentgenogram showed slight enlargement of the heart and congestive changes at the bases of the lungs. An electrocardiogram showed small T waves in all leads and slurring of the QRS complexes in leads 2 and 3.

Biopsy of the Quadriceps Muscle and Overlying Skin.—The skin showed atrophy of the epidermis with loss of appendages. In the section of muscle there were characteristic proliferative and degenerative changes of the fibers, with collections of lymphocytes and histiocytes in the interstitial tissue, mainly about the vessels.

Course in the Hospital.—The patient was digitalized and given salicylates. The dyspnea diminished, and the pulse rate became normal. There was no fever. He was discharged after nine days. Several weeks later he was examined again. There was a papular pink rash on the trunk and extremities. On the forearms the rash tended to form circinate lesions. Muscular tenderness persisted.

CASE 7.—W. H., a 61 year old white farmer, was well until five weeks prior to his admission to the hospital, when there was a sudden onset of severe aching pain in the back of the neck and mild sore throat. Within a few hours pains occurred in the shoulders, upper extremities and abdomen and to a lesser extent in the lower extremities. The patient was obliged to go to bed, where he remained. In the muscles and

joints there were constant pain and stiffness, which were worse in the morning. There were intermittent swelling and redness of the fingers and toes. The sore throat persisted. Five days before admission, chills, fever and sweats developed. Throughout the entire five week period there was anorexia, and the patient lost 20 pounds (9 Kg.) in weight. No rash was observed. The patient experienced slight hoarseness and dysphagia and attributed these symptoms to his sore throat.

Ten years prior to admission the patient had measles followed by a mild chronic cough. During this period there were also occasional asthmatic attacks, particularly during the summer.

Physical Examination.—The patient appeared poorly developed and poorly nourished and chronically ill. The teeth were carious. The pharynx was slightly injected. Examination of the heart and lungs revealed nothing remarkable. The edge of the liver was felt 5 cm. below the costal margin. The spleen was not palpable. There were slight atrophy of the muscles of the extremities and generalized exquisite muscular tenderness. The joints were not swollen; however, pressure over the joints of the shoulder and wrist elicited tenderness.

Laboratory Studies.—There was no anemia. The total leukocyte count was 10,000 per cubic millimeter, with a normal differential count. The corrected sedimentation rate was elevated, being 34 and 42 mm. per hour on two determinations. A roentgenogram of the right shoulder joint showed no abnormality, and one of the spine showed hypertrophic arthritis in the cervical region. In the initial electrocardiogram there was an intermittent sinoauricular block. Subsequent tracings showed normal sinus rhythm. The blood uric acid was 2.6 mg. per hundred cubic centimeters. Cultures of material from the throat did not yield pathogenic organisms. The patient's serum did not agglutinate Brucella abortus organisms. The total protein and the album-globulin ratio were normal. The basal metabolic rate was —2 per cent.

Biopsy of the Deltoid Muscle.—There were a pronounced increase of muscle nuclei and a moderate inflammatory response in the interstitial connective tissue. Many muscle fibers showed degenerative changes.

Course in the Hospital.—The patient was observed for eleven days. On the first and the second day the temperature rose to 99.6 F., and thereafter it remained normal. The pulse rate was not elevated. Determinations of the vital capacity, venous pressure and circulation times (sodium cyanide and paraldehyde) revealed normal values. On the third day salicylate therapy was begun, and this resulted in great improvement. The patient became ambulatory within a week. Muscular stiffness and tenderness persisted but were less severe.

When examined one month later, the patient still complained of muscular stiffness and slight tenderness of the muscles, but there was no swelling or tenderness of the joints. He had gained 10 pounds (4.5 Kg.) in weight.

CASE 8.—M. C., a 32 year old white woman, entered the hospital on May 1, 1942. In December 1940 she first noticed vague pains in muscles and joints. In March 1941, after extraction of many teeth, she had fever, with a temperature of 102 F., slight dyspnea, orthopnea and edema. The edema began in the lower extremities and slowly spread to involve the trunk and upper extremities but did not affect the face. There were no urinary complaints. At this time her local physician found fever, edema, an apical systolic murmur and tenderness of joints. He made a diagnosis of acute rheumatic fever and treated the patient with salicylates and digitalis in addition to rest in bed. The edema, dyspnea and orthopnea subsided within six weeks. At this time the patient began to have frequent frontal headaches and severe pains in the muscles of the left arm and forearm and in the left shoulder and elbow joints. The pains were made worse by motion, and the patient remained in bed. She continued to have an intermittent slight fever, weakness and malaise. There was occasional edema of the hands. No swelling of the joints was observed. A painless erythematous papular rash occurred intermittently about the mouth. The appetite remained good, and the patient gained 10 pounds (4.5 Kg.) in weight during the present illness.

Physical Examination.—The patient appeared well developed and well nourished. The heart was not enlarged. A rough basal and a soft apical systolic murmur were present. The liver and spleen were not enlarged. A few small red papular lesions were present about the mouth. Pain was produced by pressure over the left shoulder joint. There was muscular tenderness over the left arm and forearm, over the upper portion of the left leg and to a lesser extent in the left pectoral region. These pains were increased by motion. There was no limitation of motion and no swelling of the joints. The hands and feet showed slight puffiness.

Laboratory Studies.—On the patient's admission the hemoglobin content was 12.3 Gm. per hundred cubic centimeters and the total erythrocyte count 4,460,000 per cubic millimeter and the total leukocyte count 12,250. Differential leukocyte counts were not remarkable. The sedimentation rate was not elevated. Examination of the urine and stools showed them to be normal. The total serum protein and the albumin-globulin ratio were normal. An electrocardiogram showed no abnormality. A roentgenogram of the chest was normal, as were films of the left knee and the adjacent long bones. Culture of material from the throat showed no pathogenic organisms. Cultures of the urine and blood were sterile. Agglutination tests of the patient's serum with Br. abortus and Pasteurella tularensis gave negative results.

Biopsy of the Deltoid Muscle.—The muscle showed a moderate increase in sarcolemmal nuclei and a moderate inflammatory reaction in the interstitial connective tissue. Phagocytosis of fibers was not observed.

Course in the Hospital.—During the two week period of hospitalization the muscular pains persisted, although they varied in location and severity. On several occasions during the first week there were rises in temperature to from 99.6 to 100 F., and the pulse rate varied between 90 and 110. Thereafter the pulse rate and the temperature were normal. Determinations of the venous pressure, circulation time and vital capacity revealed them to be within normal limits. Digitalis was discontinued. Large amounts of salicylates did not relieve the muscular pains. The frontal headaches persisted. The patient was encouraged to become ambulatory. It was observed that walking short distances fatigued her but did not cause dyspnea. At the time of discharge she was instructed to take frequent warm baths and 30 mg. of alpha tocopherol (orally) daily. Her weight fell from 134½ to 125½ pounds (60.5 to 56.5 Kg.) while she was in the hospital.

One month after discharge the patient was examined again. At this time her muscular pains and exertional

dyspnea persisted and there was a loss of 8 pounds (3.6 Kg.) of weight. There was definite periorbital edema. Additional laboratory studies showed no change.

CASE 9.—L. S., a 44 year old white farmer, was first seen in the outpatient clinic of the hospital in September 1938. At that time he complained of chronic headaches and postnasal discharge. The diagnosis of sinusitis was confirmed by roentgenograms. Following treatment the sinusitis appeared to be relieved but the headaches were not affected. A psychiatric consultant was of the opinion that the patient had a schizoid personality and that the headaches were functional. The patient was not seen again until April 9, 1942, when he entered the hospital complaining of pains in muscles and joints of five months' duration. In November 1941 a dull aching pain appeared in the right shoulder and extended down the right arm. This pain, which was aggravated by motion, subsided within several weeks, and similar pain developed in the left arm. Within a month incapacitating stiffness and soreness involved the entire skeletal musculature. In March 1942 the patient first noticed that his hands and feet would become blue and painful after they were exposed to cold. At the same time there occurred edema of the hands, wrists, feet and ankles, and this was present intermittently thereafter. In addition, there were pains in the joints of the shoulders, wrists and toes. There was no appreciable loss of weight or strength.

Physical Examination.—The patient was well developed, well nourished and muscular. The skin was clear. The retinal arteries were slightly sclerotic. The heart and lungs were normal. Muscular tenderness to pressure was present over the right pectoral region, the posterior axillary folds and the trapezius muscles. There were no other abnormal physical findings.

Laboratory Studies.—There was no anemia. The total leukocyte count was 4,700 per cubic millimeter, with a normal differential count. Examination of the urine gave normal results. The sedimentation rate was slightly elevated on two of three determinations. An electrocardiogram was normal. Roentgenograms of the hands showed no abnormalities. The basal metabolic rate was normal. The total serum protein amounted to 7.84 Gm. per hundred cubic centimeters, with albumin 4.06 Gm. A biopsy of the deltoid muscle showed no abnormality.

Course in the Hospital.—In the ten day period during which the patient was observed, the pulse and temperature remained normal. The stiffness, soreness and tenderness of muscles persisted and were not relieved by acetylsalicylic acid. While in the hospital the patient lost 7½ pounds (3.4 Kg.) in weight.

The patient reentered the hospital two months after the first admission. He had continued to have severe persistent muscular pains, which interfered with sleep. There was a loss of 20 pounds (9 Kg.) of weight. The complaints were otherwise unchanged.

On examination diffuse muscular tenderness was noted. The patient was unable to abduct his arms to a horizontal position because of weakness and pain. There was definite atrophy of the musculature of the shoulder girdle and upper parts of the arms. The laboratory findings showed no appreciable change.

Biopsy of the Quadriceps Muscle.—In contrast to the previous section of deltoid muscle, this section showed pronounced changes. There were extensive sarcolemmal nuclear proliferation and extensive but variable degenerative changes in the muscle fibers. There was a moderate inflammatory reaction in the interstitial tissue.

The patient remained in the hospital several weeks and was not improved by artificial fever therapy induced by typhoid vaccine, by frequent hot baths or by oral administration of 40 mg. of alpha tocopherol daily.

COMMENT

There are certain interesting features in the cases of this small series of patients, 7 male and 2 female. Their ages ranged from 32 to 61 years. A febrile illness initiated the earliest symptoms in 2 cases, and in 2 the earliest symptoms followed recent dental extractions. The duration of the illness prior to establishment of the diagnosis varied from five weeks to eight years. Only for 1 patient (case 4) was the diagnosis of dermatomyositis made prior to admission to the hospital.

Cutaneous manifestations occurred in 7 of the 9 cases. In 5 instances there was an erythematous rash, which varied in extent, location and duration. In 4 cases there were sclerodermatous changes, which were diffuse in 1 case and in the others localized to the extremities or to the face and extremities. Focal blue-brown pigmented areas were present over the spine in 2 cases. Hyperhidrosis was noted in 1 instance. Trophic ulcers of the hands were noted in 2 patients with sclerodermatous changes. Telangiectases were prominent in 2 cases. One patient exhibited punctate erythematous lesions of the soft palate, and a second had numerous telangiectases on the palate. Edema, which most commonly occurred in the periorbital region, was present in every case.

Evidence of involvement of muscles was a constant finding. Every patient complained of muscular stiffness which was pronounced in the morning and was usually relieved by gentle exercise and made worse by prolonged or severe exertion. Subjective muscular weakness was absent in only 1 case. Three patients complained of muscular cramps which tended to be more severe at night. Three patients noticed spontaneous twitching of their muscles. Palpation of the muscles, particularly of the shoulder girdle group, elicited tenderness in every case except 1 (case 3). The consistence of the muscles was normal or reduced. In 6 patients there was demonstrable muscle atrophy, which affected most often the musculature of the shoulders and of the pelvic girdle. Involvement of nonskeletal striated muscle was less frequent. Hoarseness occurred in 4 instances; dysphagia in 2 and diplopia in 1. Six patients complained of dyspnea. In several instances other factors, such as emphysema and cardiac failure, may have produced this symptom. Fluoroscopic evidence of impairment of the motion of the diaphragm

was noted in 2 cases. Two patients had cardiac arrhythmias, which might be considered incidental findings or evidence of cardiac involvement in this disorder. In a third instance (case 6) evidence of myocardial disease preceded any symptoms referable to dermatomyositis.

A history of Raynaud phenomena was elicited in 4 cases. In 2 of these the patients had sclerodermatous changes of the hands. In a fifth case, in which the patient had diffuse scleroderma (case 5), there was no history of Raynaud phenomena yet they were readily demonstrated by temperature experiments.

Fever, usually slight, was present in 5 of the cases during the illness. Loss of weight was present in 7 cases and varied from 10 to 100 pounds (4.5 to 45 Kg.). Three patients had a chronic productive cough, which might have been secondary to disturbance of the respiratory muscles in 2 of them. Three patients complained of paresthesias. There was slight to moderate enlargement of the liver in 4 cases. Three patients had arthritic pains without localized swelling of the joints.

Retinal changes, splenomegaly, enlargement of lymph nodes, serous effusions, hemorrhagic disorders and neurologic disturbances were not observed in this series.

Therapy in these 9 cases met with little success. Oral administration of salicylates gave symptomatic relief in only 1 instance. Frequent hot baths gave temporary relief. Alpha tocopherol given orally in doses of 40 mg. daily was employed for periods of one to several months in 5 cases without significant relief. Fever therapy with typhoid vaccine gave slight improvement in 1 case but not in 2 others. Other measures were ineffective.

Few abnormal laboratory findings were present in this series. In 4 of the 9 cases there was a moderate normocytic, normochromic anemia, with the hemoglobin content varying from 10 to 12 Gm. per hundred cubic centimeters. In 7 of the 9 cases the leukocyte count was within normal limits, while in 2 cases it was elevated on repeated determinations. In the differential counts 5 per cent and 6 per cent eosinophils respectively were noted in 2 cases on single determinations, but in subsequent differential counts eosinophils were less numerous. In the remaining cases there was no eosinophilia. In 3 cases there were 8 per cent or more monocytes, and in 1 of these the monocyte count varied between 15 and 26 per cent. A moderate increase in the sedimentation rate was observed in 5 cases. Repeated examinations of urine and stools showed no abnormality in any case.

In every instance the plasma nonprotein nitrogen was normal. Determinations of the serum calcium, phosphorus and phosphatase showed them to be normal in every case. Blood sugar values (fasting) varied between 76 and 108 mg. per hundred cubic centimeters. Two patients exhibited slight elevations of the basal metabolic rate, with repeated determinations showing values between plus 10 and plus 25 per cent, while the rates of the remaining 7 patients were normal. The serum cholesterol was normal in the 5 cases in which it was determined, as was the serum chloride in the 3 cases in which it was determined. The Kahn reaction of the blood was negative in every instance. In 2 of the 9 cases the plasma protein was in excess of 8 Gm. per hundred cubic centimeters. The hyperproteinemia resulted from an increase in the globulin fraction. In a third case a slight decrease in the serum albumin together with a rise in the serum globulin resulted in a reversal of the albumin-globulin ratio. Examination of the spinal fluid, which was performed in 4 cases, showed no abnormality. Roentgenograms of the hands and feet and of the adjacent long bones showed no

TABLE 1.—*Representative Laboratory Values* *

	Studies of Blood												Studies of Urine			
				Differential Count, per Cent				Corrected Sedimentation Rate,† Mm./Hr.	Serum Protein							
Case No.	Red Blood Cells, Millions	Hemoglobin, Gm. per 100 Cc.	White Blood Cells	Neutrophils	Eosinophils	Monocytes	Lymphocytes		Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Mg. Creatine per 24 Hr.	Mg. Creatinine per 24 Hr.	Creatinine Coefficient	Number of Determinations
1	4.33	12.7	10,600	70	6	6	17	30	3.91	4.10	178	80	155	700	12.3	9
2	4.6	12.8	6,000	66	0	8	25	12	5.01	2.30	238	70	365	519	9.6	5
3	3.7	10.9	4,800	76	0	6	18	19	5.08	2.38	143	100				
4	3.63	12.0	5,400	46	2	6	46	14	4.33	2.86	...	108	247	928	15.5	1
5	4.6	11.6	15,000	72	2	3	21	28	4.10	3.06	161	90	330	944	17.0	3
6	3.7	10.2	8,700	65	0	2	33	28	2.91	6.78	151	..	320	1,050	10.5	1
7	5.1	13.0	10,000	75	3	2	18	34	3.85	4.06	...	76	633	347	6.2	1
8	4.46	12.3	12,250	80	3	1	16	26	4.67	1.86	...	108	81	292	5.0	2
9	5.04	15.2	4,600	71	0	2	26	12	4.06	3.78	...	98	300	903	12.4	2

* For blood counts and blood chemistry only single illustrative values are cited. For creatine and creatinine, average values are given.

† Wintrobe method.

abnormality in the 6 patients who had these studies.

Anemia and significant leukocytosis or leukopenia are unusual in dermatomyositis.[13] A relative increase in the number of monocytes was present in approximately 50 per cent of a large series of cases reported by Schuermann,[1b] while in 45 per cent there was a significant eosinophilia. The sedimentation rate of the blood is frequently increased, especially during an acute exacerbation.[1b] Albuminuria was present in 14 of the 40 cases of O'Leary and Waisman,[1a] and in a small number of these the urinary sediment contained erythrocytes and casts. The basal metabolic rate usually has been found normal but may be elevated.[4b] Changes in the plasma proteins are infrequent. O'Leary and Waisman [1a] noted that in 2 of 4 cases the serum protein was reduced without change in the albumin-globulin ratio. In several instances [14] cases have occurred in which the concentration of serum proteins has been normal or reduced and there has been reversal or a tendency to reversal of the albumin-globulin ratio. In a case of poikilodermatomyositis, Horn [15] found hyperproteinemia due to an increase in the globulin fraction. The studies of blood calcium and phosphorus usually have shown no abnormality, although the serum calcium was low in a case described by Richter.[16] Osteoporosis has been observed.[17] Other laboratory findings usually have been normal. Milhorat and his co-workers [12] noted a disturbance in the ratio of urinary calcium to fecal calcium in dermatomyositis.

Determinations of creatine and creatinine in twenty-four hour specimens of urine were made in 8 of the 9 cases. Multiple determinations were made in 5 cases. In every instance there was spontaneous creatinuria, the amount varying from 53 to 633 mg. per twenty-four hours. The percentage of creatine to total creatinine (preformed creatinine and creatine) varied from 10 to 65 per cent, with an average of 31 per cent. The amount of preformed creatinine was reduced in every case. The creatinine coefficient (number of milligrams of creatinine excreted in twenty-four hours per kilogram of body weight) was reduced in all the male patients, being below 18 (normal range is 18 to 32); it was within normal limits in 1 female patient (15.5) and reduced in the other (5 [normal for females 9 to 26]).

The determinations of creatine and creatinine for these patients were carried out while the patients were on diets containing 60 to 80 Gm. of protein daily. Bodansky and his co-workers [18] in a case of "generalized myositis fibrosa" found the degree of creatinuria with an ordinary diet to be identical with that noted with a creatine-free diet, although a high protein diet increased the amount of urinary creatine. This same observation was made by one of us in a case of dermatomyositis which was studied elsewhere and is not included in this group. Healthy women, particularly during the menstrual period, may excrete considerable amounts of creatine [19]; hence the finding of this substance in the urine of women may not be abnormal. Many observers have noted creatinuria in dermatomyositis. We have found no case mentioned in which studies of creatine were made in which there was not creatinuria. The great daily variations in output of creatine and creatinine which occurred in our patients has also been observed by others.[20] In general, the degree of creatinuria increases with the activity of the disease. Milhorat and his co-workers [12] observed in 2 cases of dermatomyositis that administration of wheat germ oil resulted in a decrease in urinary creatine and an increase in creatinine. In 2 instances (cases 1 and 9) prolonged administration of vitamin E had no significant effect on excretion of creatine and creatinine. In the other cases this effect was not studied.

Ergographic tracings of the combined action of finger and forearm muscles were obtained in all cases and revealed apparently normal types of fatigue curves but diminished muscular power. The degree of loss of power varied with the severity of the case. Dynamometer studies of the hand grip and of the ability of retraction of the shoulder muscles showed diminished power when contrasted with that of other subjects of the

13. O'Leary and Waisman.[1a] Schuermann.[1b]

14. Lane, C. W.: Dermatomyositis, South. M. J. **31**: 287-294 (March) 1938. Kinney and Maher.[1c] Keil.[4c]

15. Horn, R. C., Jr.: Poikilodermatomyositis: Report of Case with Complete Postmortem Examination, Arch. Dermat. & Syph. **44**:1086-1097 (Dec.) 1941.

16. Richter, R.: Exfoliative generalisierte Erythrodermie bei Dermatomyositis, Dermat. Wchnschr. **111**: 710-712 (Aug. 17) 1940.

17. (*a*) Griffiths, W. J.: Biochemical Aspects of Dermatomyositis, Brit. J. Dermat. **52**:295-304 (Oct.) 1940. (*b*) Kinney and Maher.[1c] (*c*) Milhorat, Weber and Toscani.[12]

18. Bodansky, M.; Schwab, E. H., and Brindley, P.: Creatine Metabolism in a Case of Generalized Myositis Fibrosa, J. Biol. Chem. **85**:307-325 (Dec.) 1929.

19. Smith, O. W.: Creatinine Excretion in Women: Data Collected in the Course of Urinalysis for Female Sex Harmones, J. Clin. Endocrinol. **2**:1-15 (Jan.) 1942.

20. Dilger, M.: Stoffwechseluntersuchungen bei Dermatomyositis, Ztschr. f. Kinderh. **58**:564-573, 1936. Steinitz, H., and Steinfeld, F.: Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, Ztschr. f. d. ges. exper. Med. **79**:319-328, 1931. Griffiths.[17a]

same age and sex. Loss of strength of the shoulder muscles was more pronounced than that of the hand muscles in all cases.

In 5 cases electrical stimulation of multiple muscle motor points failed to show the reaction of degeneration. In every instance, however, the amount of current necessary to produce contractions was 25 to 40 per cent greater than that required for controls. Somewhat similar observations have been made by others.[21] In 1 case (case 2), the muscle action current in response to single, paired and multiple nerve stimuli was studied with a cathode ray oscillograph by Harvey according to the method of Harvey and Maisland.[22] The muscle action current showed reduced voltage, but no other abnormality could be found.

In 6 cases studies were made of the carbohydrate metabolism. In 3 of these the dextrose tolerance test (oral) and the insulin tolerance test [23] were found to give normal results; in the other 3 these tests were not done. In all 6 cases the combined insulin and dextrose tolerance test as recommended by Himsworth [24] was employed. This procedure involves determination of simultaneous arterial (capillary) and venous sugar levels thirty and sixty minutes after oral administration of 50 Gm. of dextrose and intravenous injection of 5 units of insulin. Griffiths [17a] found that in some cases of dermatomyositis there was little difference between the arterial and the venous sugar values, particularly at thirty minutes, in contrast to results for normal persons, whose arterial sugar values are considerably greater than the venous levels. This diminished arteriovenous difference in dermatomyositis was interpreted as resulting from impaired glycogenesis in muscles under the influence of insulin. However, the 6 patients in our series failed to exhibit such a response. In every case a considerable arteriovenous difference was obtained. We employed this same test for patients with periarteritis nodosa, amyotrophic lateral sclerosis, myasthenia gravis, thyrotoxicosis, progressive muscular atrophy and myotonia dystrophica. All these had pathologic changes in the striated muscle, confirmed by biopsy. Only a single patient, one with marked hyperthyroidism, had values which might indicate reduction of the ability of muscles to form glycogen.

Studies of cutaneous temperature were made on 8 of the 9 patients. Measurements were made with a thermocouple which was sensitive to 0.5 degree (0.9 F.) C. The response of the index finger to overcooling was abnormal in 5 of the cases. Lewis [25] has found that if a finger or a finger and a portion of the hand are immersed in water at 0 to 10 C. for ten minutes vasodilatation of the exposed skin occurs during the immersion. After its withdrawal the finger recovers its original temperature within twenty minutes and then rises 1 to 6 degrees C. (1.8 to 11 degrees F.) above its original temperature and above that of the nonimmersed fingers. This elevation persists for many minutes. This is known as the reaction to overcooling and always occurs in normal subjects. Rarely the immersed forearm also shows the reaction to overcooling. In cases of severe Raynaud's disease, with or without diffuse scleroderma, Lewis observed that after immersion the chilled finger had a delayed and often incomplete return to its initial tempera-

TABLE 2.—*Values for Arterial and Venous Sugar Obtained in the Combined Insulin and Dextrose Tolerance Test*

	Fasting		30 Minutes		60 Minutes	
Case	Arterial *	Venous	Arterial *	Venous	Arterial *	Venous
1	108	96	79	53	87	74
2	144	150	188	114	160	110
5	104	100	110	86	137	119
7	80	78	105	92		
8	108	120	330	292	410	360
9	101	112	230	156	127	110

* Arterial (capillary) blood sugar.

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22. Harvey, A. M., and Maisland, R. L.: Method for Study of Neuromuscular Transmission in Human Subjects, Bull. Johns Hopkins Hosp. **68**:81-93 (Jan.) 1941.

23. Fraser, R. W.; Albright, F., and Smith, P. H.: Value of Glucose Tolerance Test, Insulin Tolerance Test, and Glucose Insulin Tolerance Test in Diagnosis of Endocrinologic Disorders of Glucose Metabolism, J. Clin. Endocrinol. **1**:297-306 (April) 1941.

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25. (*a*) Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers: A Variety of Raynaud's Disease, Heart **15**:7-101 (Aug.) 1929. (*b*) Observations upon the Reactions of the Vessels of the Human Skin to Cold, ibid. **15**:177-208 (May) 1930. (*c*) Lewis, T., and Landis, E. M.: Further Observations upon a Variety of Raynaud's Disease, with Special Reference to Arteriolar Defects and to Scleroderma, ibid. **15**:329-350 (July), 1931. (*d*) Lewis, T.: Supplementary Notes upon the Reactions of the Vessels of the Human Skin to Cold, ibid. **15**:351-358 (July) 1931.

ture with the subject at ordinary room temperature. Even in such cases the reaction to overcooling occurred if the room temperature was sufficiently high (e. g. 30 C.).

Eight patients and 10 normal controls had one forearm and hand immersed in water at 0 C. for three minutes. Prior to the immersion the subjects were allowed fifteen to thirty minutes to attain equilibrium with the room temperature at which the observations were made. During this period frequent measurements of temperature were made at selected areas. No measurements were made while the hand and forearm were immersed. After withdrawal, the forearm and hand were dried by gentle patting. Beginning one minute after withdrawal, temperature readings were obtained at two minute intervals from the palmar surface of the index finger, the dorsum of the wrist and the flexor surface of the midportion of the forearm of both the cooled and the uncooled upper extremity. In the 10 control subjects and in the 8 patients with dermatomyositis, the temperature response was identical except in the index finger of the immersed extremity. The recovery of the immersed wrist and forearm was seldom complete in twenty to thirty minutes, and usually at the end of this period the temperature was several degrees below the initial temperature. In no instance did the temperature of the chilled wrist and forearm rise above the original temperature. In the unimmersed extremity, the temperature of the index finger fell 1 to 3 degrees C. (1.8 to 5.4 degrees F.) after immersion of the other extremity, and recovery was complete two to seven minutes after withdrawal of the immersed extremity. This was interpreted as increased vasomotor tone initiated by the cold stimulus. The unimmersed wrist and forearm showed no significant change in temperature.

In the 10 control subjects without vascular disease, the index finger showed the characteristic response to overcooling. The immersed index finger returned to its original temperature at an interval varying from six to sixteen minutes after withdrawal from the bath. Recovery was followed by a rise of the temperature of the index finger from 1 to 4 degrees C. (1.8 to 7.2 degrees F.) above the original temperature and above that of the nonimmersed index finger. This rise persisted for ten minutes or longer.

In 5 of the cases of dermatomyositis the index finger failed to return to its original temperature or to the temperature of the nonimmersed index finger within twenty to thirty minutes (cases 1, 2, 3, 5 and 7). In 1 instance (case 9) recovery was delayed; however, the characteristic rise occurred. In 2 instances the response was normal. One of the patients with a normal recovery temperature response had Raynaud phenomena, while 1 of the patients with delayed recovery had no Raynaud phenomena.

The temperature studies on the controls and on the patients with dermatomyositis were made at room temperature varying from 20 to 25 C. During a given study the room temperature did not vary more than 1 degree C. Subsequent studies on 2 normal controls showed that the recovery of the chilled index finger was equally rapid at room temperatures of 20 and 25 C., although the initial skin temperature was lower at the cooler room temperature. The recovery period of the patient with diffuse scleroderma and Raynaud phenomena was much slower at 20 than at 25 C. We have also determined the

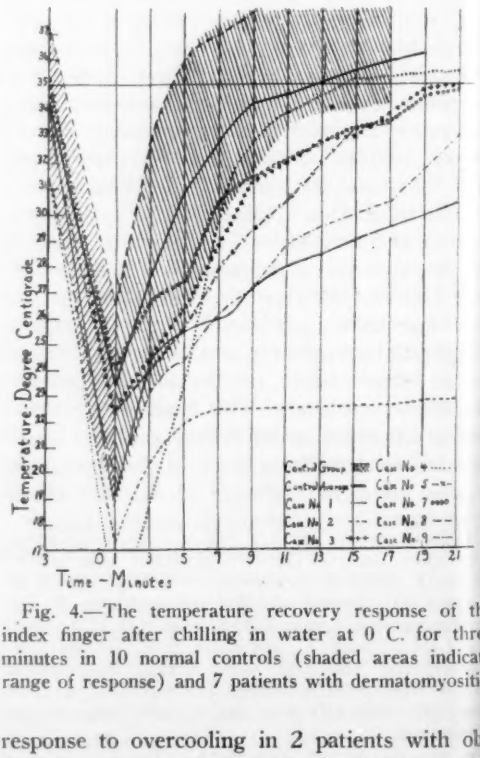

Fig. 4.—The temperature recovery response of the index finger after chilling in water at 0 C. for three minutes in 10 normal controls (shaded areas indicate range of response) and 7 patients with dermatomyositis.

response to overcooling in 2 patients with obstructive vascular disease of the large arteries of the upper extremities. In both, the recovery of the immersed index finger was delayed and there was no rise above the original temperature or above the temperature of the nonimmersed fingers.

Space does not permit an adequate discussion of the technical difficulties in obtaining reliable readings of skin temperature studies or in

interpreting them.[26] To us the observations in our cases of dermatomyositis suggest that there was an impaired flow of blood to the vessels of the skin of the fingers in 5 instances.

In 2 instances (cases 1 and 5) the patient's entire body was immersed in water at 20 C. for ten minutes. The room temperature was 25 C. In each instance the extremities showed severe cyanosis which persisted for thirty minutes after the bath. The trunk and the proximal portions of the extremities recovered before the distal parts. The temperature of the skin of the fingers did not return to the original level in thirty minutes after the bath. The production of cyanosis at 20 C. is in accord with attacks in patients with Raynaud's disease. Lewis [25a] produced typical Raynaud attacks in patients at temperatures of 15 to 20 C. It is interesting that the patient in case 5 gave no history of Raynaud phenomena although objective evidence revealed the condition.

Biopsies of skin were obtained in 4 cases, and sections of muscle were obtained in all except 1 case (case 4). All sections were routine surgical specimens which were fixed in solution of formaldehyde, embedded in paraffin and stained with hematoxylin and eosin. No special stains were employed. The sections showed atrophy of the epidermis and slight perivascular lymphocytic infiltration in the corium. None of these sections was obtained from an area exhibiting a rash. In case 5, in which clinically the patient exhibited diffuse sclerodermatous changes, the corium appeared denser than normal and partially hyalinized. No vascular lesions were observed.

The 8 biopsy specimens of muscle showed considerable histologic variation. In all there were demonstrable abnormalities. Degenerative changes of the muscle fibers, such as vacuolation, loss of striation, hyalinization, variation in staining, fragmentation and atrophy, were observed occasionally; however, we were unable to be certain that many of these changes were not artefacts in our sections. The most constant alteration was an increase in muscle nuclei. Usually the nuclear increase was of the sarcolemma type, that is, of the muscle cells lying beneath the sarcolemma membrane. In many areas there were columns of nuclei which appeared to lie in the central portions of the longitudinally sectioned fibers. These nuclei were elliptic or round and were larger and contained less chromatin substance than usual. Occasionally similar-appearing nuclei were seen in the central portions of transversely sectioned muscle fibers. In a few sections the sarcolemma nuclei showed degenerative changes, such as pyknosis and karryorrhexis. Giant cells occasionally were encountered. These consisted of large numbers of centrally placed nuclei lying in a poorly defined cytoplasmic substance. Phagocytosis of fibers by mononuclear cells was observed frequently. The degree of inflammatory response in the interstitial tissue was variable but usually slight. The cells were predominantly histiocytes and lymphocytes, although plasma cells and polymorphonuclear leukocytes occasionally were encountered. In 2 instances small amounts of brown pigment granules were observed in the interstitial tissue. Perivascular inflammatory cells were present in every section but usually were not numerous. In many sections there was an apparent focal increase in interstitial tissue. The small arteries and arterioles usually appeared normal, although in a few instances there was moderate thickening of the media. No vessel showed proliferative or necrotizing changes or infiltration of the wall with leukocytes.

In an effort to determine the specificity of the histologic changes of dermatomyositis, we examined a number of surgical biopsy specimens from patients with other conditions. This group included 4 sections of normal muscle removed during surgical operations and sections of muscle from 1 patient with torticollis, 2 patients with lupus erythematosus disseminatus, 4 with acute rheumatic fever, 1 with acute glomerulonephritis, 1 with chronic glomerulonephritis, 1 with malignant hypertension, 1 with Volkmann's contracture, 3 with periarteritis nodosa, 1 with thyrotoxicosis with marked muscular atrophy and 1 with myotonia dystrophica. In many of these sections there were apparent degenerative changes, such as atrophy of the fibers, vacuolation of the cytoplasm, loss of striation, fragmentation of the fibers and variation in staining of the fibers. In addition, an apparent slight focal increase in muscle nuclei was encountered frequently.

In the 3 specimens of muscle from patients with periarteritis nodosa, characteristic vascular lesions were present. In addition, in each instance there were extensive focal increase in muscle nuclei, nuclear degenerative changes, phagocytosis of fibers, interstitial inflammatory changes and focal increase in interstitial connective tissue. In biopsy specimens from 1 of the 2 patients with lupus erythematosus, 1 of the 4 patients with acute rheumatic fever and the

26. Cobet, R.: Die Hauttemperatur des Menschen, Ergebn. d. Physiol. **25**:439-516, 1926. Weatherly, J. H.: Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, Am. Heart J. **24**:17-30 (July) 1942.

patient with myotonia dystrophica, the muscle showed degenerative, proliferative and interstitial changes which were not distinguishable from the changes in our cases of dermatomyositis.

There is general agreement that the histologic changes in the skin in dermatomyositis are nonspecific. The usual alterations are atrophy of the epidermis, edema and perivascular infiltra-

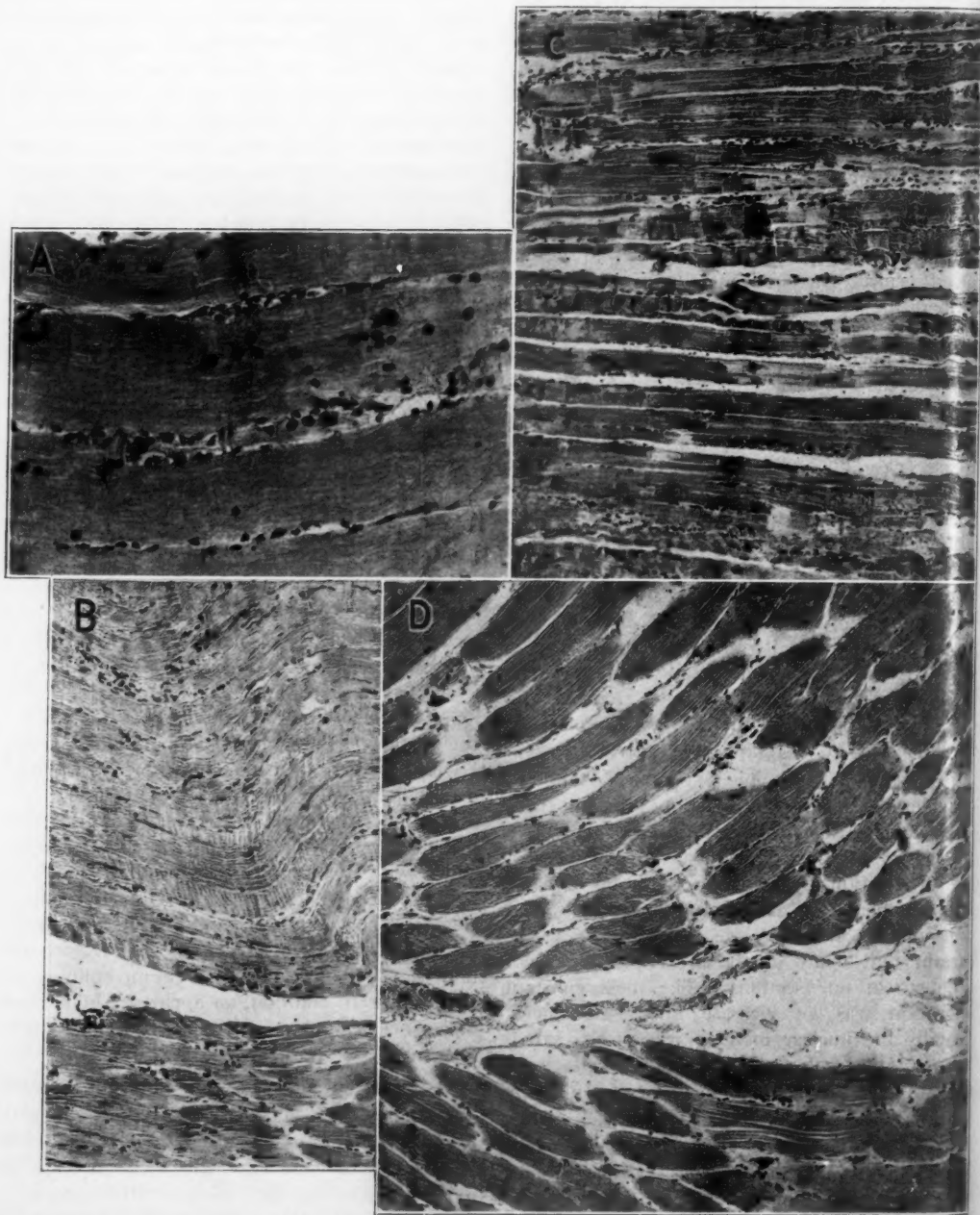

Fig. 5.—Biopsy specimens of muscle: *A*, from case 1; note the apparent phagocytosis of necrotic muscle fiber. *B*, from case 2; note the nuclear proliferation and the slight interstitial inflammatory reaction. *C*, from a case of disseminated lupus erythematosus; there are extensive proliferation of muscle nuclei and a slight interstitial inflammatory reaction. *D*, from a case of myotonia dystrophica; note the muscle giant cells and the nuclear proliferation.

tion of the corium with lymphocytes and plasma cells. The vessels of the corium may be narrowed.

In the muscle similar pathologic changes have been reported by many observers.[27] The degree of involvement is variable. Certain muscles or portions of muscle may not be involved; hence negative results of biopsy do not exclude this diagnosis. This was observed in case 9 of our series, in which the initial biopsy specimen showed no change while a second specimen showed the usual changes. There may be hemorrhage into the muscle. The interstitial connective tissue may be edematous or increased in amount. A variable degree of infiltration with inflammatory cells, mainly lymphocytes, occurs in the interstitial tissue. Occasionally lymphoid follicles ("lymphorrhages") [9a] may be present. The arterioles may appear normal. Often they appear dilated. The walls of the vessels may be thickened and may show extensive changes.[28] The muscle fibers show proliferative and degenerative changes. Muscle giant cells may occur, and sarcolemma nuclei may be increased. Degenerative changes in the muscles include edema of the fibers, loss of striation, fragmentation, atrophy, necrosis with phagocytosis, and hyaline, granular, fibrinous and vacuolar degeneration.

These histologic changes in the muscle are not specific for dermatomyositis. Similar muscle changes in muscles have been observed in many other diseases, such as rheumatoid arthritis,[29] pneumonia,[30] thyrotoxicosis [31] and a variety of other disorders.[27]

27. von Meyenburg, H.: Die quergestreifte Muskulatur, in Henke, F., and Lubarsch, O.: Handbuch der Speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, pt. 1, pp. 299-508. O'Leary and Waisman.[1a] Kinney and Maher.[1c] Keil.[1d] Keller.[2a]

28. Keil.[1d] Keller.[2a]

29. Curtis, A. C., and Pollard, H. M.: Felty's Syndrome: Its Several Features, Including Tissue Changes, Compared with Other Forms of Rheumatoid Arthritis, Ann. Int. Med. **13**:2265-2284 (June) 1940.

30. Forbus, W. D.: Pathologic Changes in Voluntary Muscle: I. Degeneration and Regeneration of the Rectus Abdominis in Pneumonia, Arch. Path. **2**:318-339 (Sept.) 1926.

31. Dudgeon, L. S., and Urquhart, A. L.: Lymphorrhages in Muscles in Exophthalmic Goitre, Brain **49**: 182-186 (June) 1926. Freudenthal.[9a]

SUMMARY

In 9 new cases of dermatomyositis in adults described in this report evidence of involvement of muscles was present in every instance. Frequently there were tenderness, weakness and atrophy of skeletal muscles. Occasionally the so-called vital striated muscles of deglutition and respiration were affected. In all instances biopsy specimens of skeletal muscles revealed certain histologic changes. Evidence is presented to indicate that these microscopic lesions are not specific for this disorder.

Involvement of the skin occurred in 7 of the 9 cases. In 2 instances the mucous membranes of the mouth were affected. In 1 case there was diffuse scleroderma, and in 2 others sclerodermatous changes were confined to the hands. A history of Raynaud phenomena was elicited for 4 patients.

Extensive laboratory studies revealed no constant abnormality other than spontaneous creatinuria. Carbohydrate metabolism, as indicated by several types of tests, was apparently normal. Studies of the reaction to overcooling as shown by the cutaneous temperature gave results typical of Raynaud's syndrome in the 4 patients with a history of this disturbance and in 1 additional patient without such a history.

The variability of the manifestations in this series of cases was sufficient to arouse doubt as to whether "dermatomyositis" is a single clinical entity. A similar view is obtained from reading previous reports of cases of this disorder. In addition to clinical, laboratory and pathologic data, it may be necessary to follow the course of the illness for a prolonged period before the diagnosis may be established with certainty.

Dr. Dawson of the Pathology Department of Vanderbilt Hospital, Dr. King of the Physiology Department, Dr. Mason of the Biochemistry Department, and Dr. Youmans of the Department of Medicine, gave suggestions and assistance in this study.

Department of Medicine, Vanderbilt University.

STUDIES IN ACUTE MYOCARDIAL INFARCTION

III. DIAGNOSIS AND LOCATION OF THE INFARCT BY ELECTROCARDIOGRAM

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In previous papers [1] we have considered the clinical and laboratory features presented by 378 cases of acute myocardial infarction. The excellent early discussions of the topic [2] so emphasized the clinical aspects that myocardial infarction should be, as Henry Christian described it,[2e] "an easily diagnosable condition." In the great majority of cases the diagnosis of acute infarction of the myocardium can be made, or at least suspected, on clinical evidence alone. However, the list of conditions considered in the differential diagnosis of acute infarction is lengthy (Herrick [3] has mentioned 28). We found that but 50 per cent of our patients were admitted with the diagnosis of acute infarction and that in 20 per cent of the cases the admission diagnosis contained no mention of the heart whatsoever.[1a] The electrocardiogram therefore must play a major role in confirming the clinical diagnosis or in revealing the presence of an unsuspected infarction. As part of our study we decided to consider the value and accuracy of the electrocardiogram in the diagnosis of acute myocardial infarction.

MATERIAL AND SELECTION OF CASES

During the period from Jan. 1, 1929 to Dec. 31, 1941, 508 patients were discharged from the hospital or died with a final diagnosis of acute myocardial infarction. With the exception of 20 cases that we felt had a typical clinical picture (history, friction rub, etc.), no case formed part of this study unless there were diagnostic electrocardiographic or necropsy changes. The use of chest leads was begun at Jewish Hospital shortly after their recommendation by Wolferth and his associates.[4] Every case included on the basis of the electrocardiogram alone was reviewed by the senior author. No electrocardiogram was considered diagnostic unless it presented the changes recommended by Levine,[5] Wolferth and his co-workers [6] and Katz.[7] With these diagnostic criteria, a number of cases of sudden death were eliminated because necropsy was not done. Many cases of old infarction were not included because the electrocardiogram did not exhibit characteristic evidence of a new infarction. There remained for consideration 378 cases.

Electrocardiographic diagnoses were classified under the following headings: (1) anterior infarction, (2) posterior infarction, (3) anteroposterior infarction, (4) infarction present but location uncertain, (5) electrocardiogram not diagnostic and (6) bundle branch block. At necropsy the cases were divided into instances of anterior, of posterior and of anteroposterior infarction.

THE ELECTROCARDIOGRAPHIC DIAGNOSIS

One must be aware of the possibilities and limitations of electrocardiography. Abnormal electrocardiograms have been obtained for human beings as early as one hour and as late as twenty days after the acute attack. Barnes [8] stressed the fact that absence of diagnostic electrocardiographic changes is due to (1) failure to take sufficient tracings, (2) the presence of mul-

1. Baer, S., and Frankel, H.: Studies in Acute Myocardial Infarction: I. The Clinical Picture, Ann. Int. Med. **20**:108 (Jan.) 1944; II. Laboratory Procedures as Diagnostic Aids, ibid. **20**:115 (Jan.) 1944.

2. (*a*) Herrick, J. B.: Clinical Features of Sudden Obstruction of Coronary Arteries, J. A. M. A. **59**: 2015 (Dec. 7) 1912. (*b*) Levine, S. A., and Tranter, C. L.: Infarction of Heart Simulating Acute Surgical Abdominal Conditions, Am. J. M. Sc. **155**:57 (Jan.) 1918. (*c*) Wearn, J. T.: Thrombosis of the Coronary Arteries, ibid. **165**:250 (Feb.) 1923. (*d*) Gardiner, H. C.: Coronary Arterial Occlusion, ibid. **168**:181 (Aug.) 1924. (*e*) Christian, H. A.: Cardiac Infarction: An Easily Diagnosable Condition, Am. Heart J. **1**:129 (Dec.) 1925. (*f*) Hamman, L.: Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**: 273 (April) 1926.

3. Herrick, J. B.: On Mistaking Other Diseases for Coronary Thrombosis, J. M. Soc. New Jersey **32**: 590 (Oct.) 1935.

4. (*a*) Wolferth, C. C., and Wood, F. C.: Electrocardiographic Diagnosis of Coronary Occlusion by Chest Leads, Am. J. M. Sc. **183**:30 (Jan.) 1932. (*b*) Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion, Arch. Int. Med. **52**:752 (Nov.) 1933.

5. Levine, S. A.: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1936.

6. Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle, Arch. Int. Med. **56**:77 (July) 1935. Footnote 4.

7. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941.

8. Barnes, A. R.: Electrocardiogram in Myocardial Infarction, Arch. Int. Med. **55**:467 (March) 1935.

tiple fresh infarctions, (3) the presence of bundle branch block, (4) the presence of pericarditis and (5) a critically ill patient. In a series of 34 cases Feil, Cushing and Hardesty[9] found the electrocardiogram diagnostic in 80 per cent.

Electrocardiograms were taken for 321 of our patients (table 1). For all but 18, or 94 per cent, a diagnosis of acute myocardial infarction was made. Of the 18 for whom this was not done, 13 had only one electrocardiogram taken and 5 were given a diagnosis of bundle branch block. We see no reason to disagree with Barnes,[8] who stated that repeated electrocardiograms should reveal the infarction in practically every case.

One of the more controversial topics in this field has been the localization of the acute myocardial infarction. Wood and his associates[4b] found anterior infarction a bit more common than

TABLE 1.—*Location of Acute Infarction by Electrocardiogram*

	Cases		Deaths	
	Number	Percentage of Total	Number	Percentage
Anterior	167	52	47	28
Posterior	108	34	22	20
Anteroposterior	7	2	2	28
Acute infarction, location uncertain	21	7	6	28
Electrocardiogram not diagnostic	13	4	9	69
Bundle branch block	5	1	5	100
Totals	321	100	91	28

posterior, and Willius[10] reported anterior infarction in 56.3 per cent of his cases and posterior in 43.7 per cent. Rosenbaum and Levine[11] also found anterior infarction more frequent. In a necropsy study Bean[12] reported that 71 per cent of the infarcts were located in the anterior and apical portions of the left ventricle. In contrast to these figures, Barnes and Ball[13] in unselected autopsy material found little difference in the occurrence of anterior and posterior infarction, and Master, Jaffe and Dack[14] reported an almost identical frequency.

The distribution of our cases can be seen in the chart and in tables 1 and 2. There were 201 cases of anterior and 118 of posterior infarction. It would seem that acute myocardial infarction occurs more often in the anterior portion of the

TABLE 2.—*Distribution of 378 Cases of Acute Infarction*

	Recovered	Died	Total
Anterior infarction:			
Electrocardiogram only	120	29	149
Electrocardiogram and necropsy	...	28*	28
Necropsy only	...	24	24
Total cases			201
Posterior infarction:			
Electrocardiogram only	86	15	101
Electrocardiogram and necropsy	...	5	5
Necropsy only	...	12	12
Total cases			118
Anteroposterior infarction:			
Electrocardiogram only	5	2	7
Electrocardiogram and necropsy	...	4*	4
Necropsy only	...	1	1
Total cases			12
Infarction present location uncertain	15	4	19
Electrocardiogram not diagnostic	4	1	5
Bundle branch block	...	3	3
No electrocardiogram or necropsy	...	20	20

* See text.

left ventricle. These figures are statistically significant.[15]

This difference becomes even more striking when the cases studied at necropsy are considered (table 3). Of the 74 fatal cases in which autopsy was done, 52, or 70 per cent, were instances of anterior infarction, 23 per cent of posterior and 7 per cent of anteroposterior. These percentage differences are highly significant statistically. The question arises why the incidence of anterior infarction at necropsy was even greater than that found by electrocardiograms alone.

The answer to this is not difficult to obtain. In table 1 it is seen that definite location of the

TABLE 3.—*Location of Acute Infarction at Necropsy*

	74 Cases	Percentage of Total
Anterior	52	70
Posterior	17	23
Anteroposterior	5	7

infarct could not be made by electrocardiogram in 39 of 321 cases (12 per cent). Twenty of the 39 patients died, and autopsy was performed on 12. Of these 12 patients, 11 were found to have anterior infarction and 1 anteroposterior infarction. This is in keeping with the finding of

9. Feil, H.; Cushing, E. A., and Hardesty, J. T.: Accuracy in the Diagnosis of Myocardial Infarction, Am. Heart J. **15**:721 (June) 1938.

10. Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:189 (May 30) 1936.

11. Rosenbaum, F. F., and Levine, S. A.: Immediate Prognosis of Acute Myocardial Infarction, Arch. Int. Med. **68**:913 (Nov.) 1941.

12. Bean, W. B.: Infarction of Heart: III. Clinical Course and Morphological Findings, Ann. Int. Med. **12**:71 (July) 1938.

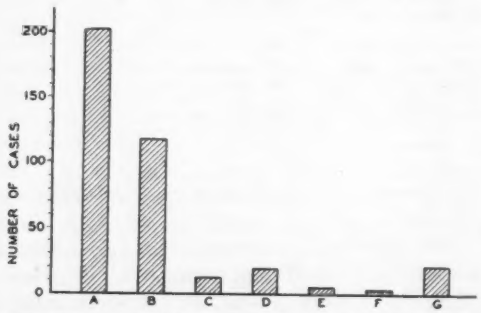
13. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Post Mortem Examinations, Am. J. M. Sc. **183**:215 (Feb.) 1932.

14. Master, A. M.; Jaffe, H. L., and Dack, J.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, Am. Heart J. **12**:549 (Nov.) 1936.

15. Pearl, R.: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1940.

Wood, Bellet, McMillan and Wolferth,[4b] who stated that most of the infarcts missed by electrocardiograms are anterior.

Another factor that would increase the autopsy incidence of anterior as compared with posterior infarction is the greater mortality of anterior myocardial infarction. We plan to consider specifically the factors influencing mortality in a separate paper. It can be seen from table 2, however, that 81 of our 201 patients with anterior infarction (40 per cent) died, as contrasted to 32, or 27 per cent, of the 118 patients with posterior infarction. This difference is of significance statistically. The question of the relative mortality of anterior and posterior myocardial infarction has been controversial. Wood and his associates,[4b] VanderVeer and Brown[16] and Stroud[17] have all expressed the opinion that anterior myocardial infarction is far more serious



Distribution of 378 cases of acute infarction according to location: *A*, anterior infarction; *B*, posterior infarction; *C*, anteroposterior infarction; *D*, location not certain; *E*, electrocardiogram not diagnostic (no autopsy); *F*, bundle branch block (no autopsy); *G*, diagnosis on clinical evidence (no autopsy).

than posterior. Master and his associates,[14] on the other hand, stated that the prognosis of anterior and that of posterior infarction are about equal, and Willius[10] said that the situation of the infarct has little influence on death or survival. Rosenbaum and Levine[11] agreed with this. It is of course true that a number of factors influence the mortality in the individual case of myocardial infarction. But by and large we feel, as have the observers cited,[18] that a patient with an anterior myocardial infarction has less chance of recovery than one with an infarct on the posterior surface of the left ventricle.

16. VanderVeer, J. B., and Brown, L. E.: The Diagnosis and Prognosis of Coronary Occlusion, Pennsylvania M. J. **39**:303 (Feb.) 1936.

17. Stroud, W. D., in discussion on Levine, S. A., and Levine, H. D.: Electrocardiographic Study of Lead IV, with Special Reference to Findings in Angina Pectoris, Tr. A. Am. Physicians **50**:303, 1935.

18. Wood and others.[4b] VanderVeer and Brown.[16] Stroud.[17]

THE ACCURACY OF THE ELECTROCARDIOGRAM

Another topic considered in this study was the accuracy of the electrocardiogram. Feil, Cushing and Hardesty[9] expressed the opinion that it is accurate in 100 per cent of acute single infarctions. A correlation of our autopsy and electrocardiographic material revealed 16 cases in which the electrocardiogram did not correctly localize the infarct (table 4). These cases were included under their correct category in table 2 (see asterisks).

Of the 16 patients, 8 had but one cardiogram taken before death, 2 had a bundle branch block and 2 were given a diagnosis of acute infarction of uncertain location. Therefore, their cases should not justly be considered as instances of electrocardiographic errors, as Barnes has emphasized.[8] Of the remaining patients, 3 had anteroposterior infarctions that were partially but not completely diagnosed. In just 1 case (interpreted as one of posterior and found to be one of anterior infarction) was there a definite diagnostic error. It seems justifiable to state that the localization of an acute myocardial infarction by the electrocardiogram is a highly accurate procedure.

COMMENT

It is difficult to explain the differences of opinion concerning the incidence and mortality of anterior and of posterior infarction.

The published series of cases of acute infarction have been sufficiently large to eliminate the errors incident to random sampling. The methods of selecting the cases cannot entirely explain these differences. The same observers[10] that reported a greater incidence of anterior infarction found little difference between the mortality of

TABLE 4.—*Discrepancy Between Electrocardiographic and Autopsy Evidenced in 16 Cases*

No. of Cases	Electrocardiographic Diagnosis	Autopsy Diagnosis
7.	Myocardial disease (only one tracing taken)	Anterior infarction
2.	Bundle branch block	Anterior infarction
2.	Acute infarction, location not certain	Anterior infarction
2.	Anterior infarction	Anteroposterior infarction
1.	Posterior infarction	Anteroposterior infarction
1.	Posterior infarction	Anterior infarction
1.	Myocardial disease old infarction (only one tracing taken)	Anteroposterior infarction

anterior and that of posterior infarction. Further detailed autopsy studies may help clarify this topic, as would more exact descriptions of the acute attack, of the location of the arterial thrombosis and of the position of the myocardial necrosis. It is noteworthy that our postmortem

19. Willius.[10] Rosenbaum and Levine.[11]

incidence of anterior infarction is identical to the 71 per cent of anterior and apical infarction found by Bean [12] at autopsy.

As far as therapy is concerned, these differences are purely academic. But they are of some importance in helping determine the prognosis of the individual case. Considering our data, we find it difficult to avoid the conclusion that anterior infarctions occur oftener than posterior and are more serious.

SUMMARY AND CONCLUSIONS

The diagnosis and location of the infarct were considered in 378 cases of acute myocardial infarction. Electrocardiograms taken in 321 cases revealed the presence of infarction in 94 per cent. On electrocardiographic study alone, 52 per cent of the infarcts were found to be anterior and 34 per cent posterior. Of 74 patients coming to necropsy, 70 per cent had anterior, 23 per cent posterior and 7 per cent anteroposterior infarction.

Anterior myocardial infarctions are more frequent and more serious than posterior infarctions. Infarction of the anterior wall of the left ventricle is more apt to be missed by electrocardiograms than posterior involvement. Electrocardiographic diagnosis and location of the infarction are highly accurate.

Completion of this study would have been impossible without the assistance and advice of Dr. Harold L. Goldburgh, Dr. A. Margolies and Dr. Joseph C. Doane.

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LIFE EXPECTANCY AFTER AN ATTACK OF MYOCARDIAL INFARCTION

REPORT OF A CASE OF SURVIVAL FOR NINETEEN YEARS AFTER CORONARY THROMBOSIS

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Initially, myocardial infarction resulting from coronary occlusion was regarded as a rapidly fatal condition. This impression was probably well substantiated by the diagnoses of preelectrocardiographic days, seldom made except in cases of the most severe form. This attitude persists despite the numerous more optimistic prognosticators; perhaps it is best that all clinicians have a wholesome respect for this serious disease and that therefore they be more than ordinarily cautious in its treatment. On the other hand, one must realize the virtue of presenting a favorable life expectancy to the patient recovering from myocardial infarction. Herrick [1] was the first (1912) to lend a gleam of hope to the situation by assuming the possibility of a long period of survival after recovery.

Electrocardiography clarified the diagnostic difficulty; the development of the method was rapid, and its accuracy has been proved, so that statistical evaluation of the life expectancy after recovery from myocardial infarction is now possible. With the advent of the electrocardiographic method, reports of five year survivals appeared in the literature. Then Burton and his associates [2] reported a case of the condition verified by necropsy in which the patient survived seven years. Jegorow [3] presented a case of multiple infarction verified post mortem in a man whose initial attack occurred fifteen years before. Conner and Holt [4] claimed to have seen a case in which the patient survived seventeen years, but they lack pathologic confirmation. White,[5] in 1933, reported his case of the disease, confirmed by autopsy, in which the patient survived for seventeen and a half years, and, in 1936, he claimed a new record of survival for twenty-four years [6] after an attack of coronary thrombosis.

With the general acceptance of such notable work, one hesitates to question White's reliability as a chronologist. However, in reviewing his two reports, we find a weakness nonexistent in our study: His 2 patients were assumed to have the initial attack of coronary occlusion on the basis of the history alone and in the course of their years of survival had other such episodes, but there were no electrocardiographic studies. We feel justified in reporting the present case, for a search of the literature shows that it is the first instance of myocardial infarction due to coronary thrombosis in which there was electrocardiographic confirmation at the onset and in which the patient lived for so long a time, nineteen years and thirty days from the initial occlusion until his death, from thrombosis, both the initial and the terminal attack being confirmed by autopsy.

REPORT OF CASE

History.—R. J. S., an attorney who was known to have hypertension, experienced a typical attack of coronary occlusion in February 1924, at the age of 42. The diagnosis was confirmed by progressive electrocardiographic changes and was concurred in by the attending physician, Dr. Sidney K. Simon, and by two cardiologic consultants, Dr. B. R. Heninger and Dr. J. B. Elliott.

An acceptable regimen was adhered to, with six weeks' rest in bed and eight months' abstinence from work. Adjusting himself well to his disability, the patient resumed partial activity and gradually returned to his legal practice on a restricted basis. For nineteen years he was under close medical observation. He experienced frequent episodes of anginoid pain, which were relieved by use of analgesics and of drugs to dilate the coronary vessels. On several occasions he had severe, prolonged transthoracic pain, with mild circulatory collapse, but never had a frank episode of congestive heart failure. Numerous electrocardiographic studies were made, the only significant change after the initial series being a progressive shift from a normal deflection to a pro-

From the Department of Medicine, Tulane University of Louisiana School of Medicine, and Touro Infirmary.

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**: 2015 (Dec. 7) 1912.

2. Burton, J. A. G.; Cowan, J.; Kay, J. H.; Marshall, A. J.; Rennie, J. K.; Ramage, J. H., and Teacher, J. H.: Fibrosis of the Myocardium with Electrocardiographic and Postmortem Examinations, Quart. J. Med. **23**:293, 1930.

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4. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**:705, 1930.

5. White, P. D.: Longevity After Coronary Thrombosis, J. A. M. A. **100**:233 (Jan. 28) 1933.

6. White, P. D.: A New Record in Longevity After Coronary Thrombosis, J. A. M. A. **108**:1796 (May 22) 1937.

nounced left axis deviation. The roentgenographic silhouette did not change in either the anteroposterior or the lateral projection, and the measurements remained within normal limits.

He lent himself well to medical interest and was seen by numerous prominent internists, all of whom concurred in the diagnosis of myocardial infarction due to coronary occlusion.

In July 1924 Dr. Emanuel Libman, who saw the patient in consultation, agreed to the diagnosis of myocardial infarction and suggested the possibility of ventricular aneurysm, but added: "There is not enough evidence for a definite diagnosis of secondary aneurysm of the heart." Drs. Hubert Schoonmaker, Franz Groedel, John Musser and W. W. Hamburger all made confirmatory reports.

On three occasions it was necessary to give the patient a large dose of sulfathiazole—once for nasofacial cellulitis, resulting from nasal furunculosis, and twice for severe prostatitis. He withstood this medication well.

Throughout the years he was a prominent, active, successful attorney and teacher.

On March 15, 1943, while in court, he experienced a typical attack of coronary thrombosis. The earliest reading of the blood pressure was 70 systolic and 30 diastolic (previous average reading 185 systolic and 90 diastolic). Oxygenation and sedation, infusion of a concentrated solution of dextrose and limited, but adequate, administration of fluids were the initial therapeutic measures. Twenty-four hours later he experienced pain on the right side of the thorax and hemoptysis (considered indicative of pulmonary infarction). The patient recovered from the immediate shock and did well for four days; then anuria developed and was successfully combated with various measures, including administration of plasma. The sequence of events was congestive heart failure, which enforced digitalization, and terminal peripheral vascular collapse, with death on the fifteenth day after the onset of the attack.

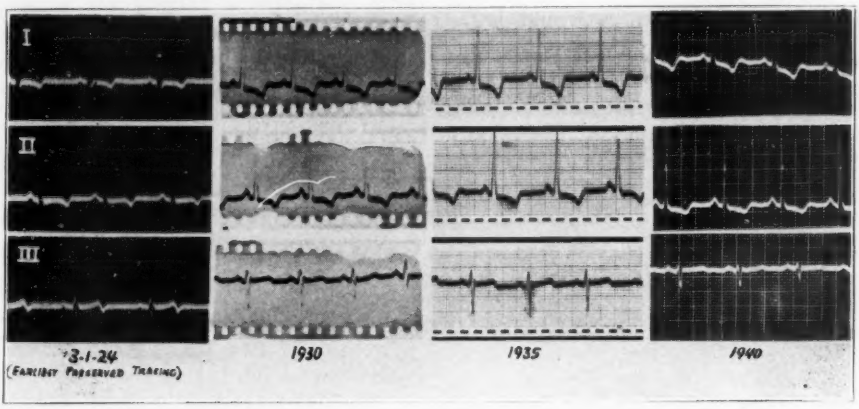

Fig. 1.—Electrocardiograms taken at intervals during the period of survival after myocardial infarction (1924-1943).

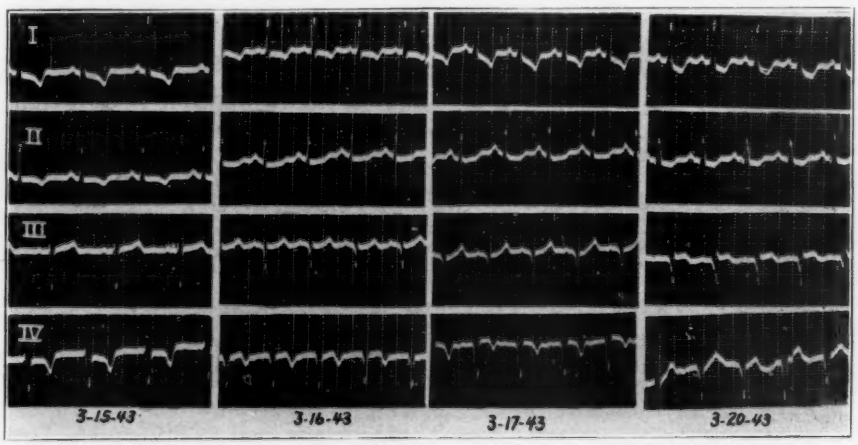

Fig. 2.—Electrocardiographic tracings taken during the terminal illness with coronary thrombosis. The patient died March 30, 1943.

Autopsy.—The heart was enlarged, weighing 575 Gm. There were moderate hypertrophy and dilatation of the left ventricle, absence of any valvular lesion and two definite areas of scarring on the left ventricle, indicative of old, well healed infarcts. The anterior descending branch of the left coronary artery was occluded 3 cm. from its origin, resulting in an area of infarction, measuring approximately 3 by 2 cm., in the anteroinferior portion of the intraventricular septum, as well

as an area in the adjacent anterior wall of the left ventricle, 2 cm. in diameter.

Microscopic study revealed definite signs of old myocardial scarring, as well as the evidence of recent infarction.

The other observations at necropsy were merely incidental. There was no ventricular aneurysm. The lungs showed only areas of atelectasis; most of the alveoli were filled with so-called heart failure cells.

COMMENT AND CONCLUSION

We shall not review the literature or compile a statistical report. Master, Dack and Jaffe [7] adequately performed this task in 1939, when they published a study of 500 cases of coronary occlusion from Mount Sinai Hospital, with a bibliography covering 2,803 clinical reports and 1,241 necropsy studies.

We have not attempted to compute an average period of survival for myocardial infarction, but we hope by reporting this interesting case to lend credence to White's contention that survival and physical activity are possible years after an attack of acute coronary occlusion and that the prognosis for all victims should be considered from this optimistic point of view.

1534 Aline Street.

7. Master, A. M.; Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, Arch. Int. Med. **64**:767 (Oct.) 1939.

PALINDROMIC RHEUMATISM

A "NEW," OFT RECURRING DISEASE OF JOINTS (ARTHRITIS, PERIARTHRITIS, PARA-ARTHRITIS) APPARENTLY PRODUCING NO ARTICULAR RESIDUES—REPORT OF THIRTY-FOUR CASES; ITS RELATION TO "ANGIO-NEURAL ARTHROSIS," "ALLERGIC RHEUMATISM" AND RHEUMATOID ARTHRITIS

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We wish to describe an unusual, oft recurring disease of joints and adjacent tissues, 34 cases of which have been studied in the arthritis service of the Mayo Clinic since 1928. Its outstanding features are multiple afebrile attacks of acute arthritis and periarthritis, and sometimes also of para-arthritis, with pain, swelling, redness and disability generally of only one, but sometimes of more than one, small or large joint, in an adult of either sex. The attacks appear suddenly and develop rapidly. They generally last only a few hours or days and then disappear completely, but they recur repeatedly at short or long, *irregularly* spaced intervals. Despite the frequent recurrences and the transitory presence (in some cases at least) of an acute or subacute inflammatory polymorphonuclear exudate in the articular tissues and cavity, little or no constitutional reaction or abnormality is revealed by laboratory tests, and no significant functional, pathologic or roentgenographic residues occur even after years of disease and scores of attacks.

The disease has not been described in any of the many new and old textbooks on articular conditions which we have examined. In certain ways it resembles, and in other ways it differs from, conditions described in 1911 and 1913 by Solis-Cohen [1] and in 1939 by Kahlmeter.[2] The resemblances of our cases to, and their differences from, those of Solis-Cohen and of Kahlmeter will be noted hereafter.

ILLUSTRATIVE CASES

Six typical cases are described in detail. Data on the remaining 28 cases and on these 6 cases are presented in table 1 and summarized in the text.

CASE 1 (table 1).—*First recognized case of palindromic rheumatism in this series.*

A woman aged 21 came to the Mayo Clinic Aug. 2, 1928, complaining of "arthritis" of eight years' duration. Her first attack was at the age of 13 years (August 1920), nine months before her first menses. Suddenly both big toes and a knee became swollen, red and painful. The attack lasted about a week; then the joints recovered completely. A month later she began to have a series of attacks which successively involved any one of several joints almost continuously during 1920 and 1921. The great toe and metacarpophalangeal joints usually were affected. Generally only a single joint was affected at one time and then only for twelve to thirty-six hours. There would be, for example, much swelling and "vicious pain" in a joint in the morning; then suddenly in the afternoon that joint would become completely well, without even residual tenderness, until its reinvolvement a few days later, but some other joint would be affected meanwhile. Attacks occurred in some joint or other almost daily; when the feet were affected she often had to stay off them because of severe pain. With attacks appearing or subsiding almost daily, she estimated that she had several hundreds of them during 1920 and 1921, and yet after each attack the affected joint became "completely well every time." Then the disease changed its pace, and the pattern of attacks altered notably.

During 1922 and 1923 the patient had only four or five attacks or small "groups of attacks" yearly. One joint of a toe or finger would be affected for two or three days; pain was severe enough to keep her awake and limit her activities temporarily. Then she would

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Presidential address presented by Dr. Hench at a meeting of the American Rheumatism Association in New York, June 10, 1940; also presented at a meeting of the Central Society for Clinical Research in Chicago, Nov. 8, 1941.

1. Solis-Cohen, S.: Certain Angioneurotic Manifestations in and Around Joints, Frequently Mistaken for Gout and Rheumatism, Tr. Coll. Physicians, Philadelphia **33**:309-311, 1911; On Some Angioneural Arthroses (Periarthroses, Pararthroses) Commonly Mistaken for Gout or Rheumatism, Tr. A. Am. Physicians **28**:739-757, 1913; Am. J. M. Sc. **147**:228-243 (Feb.) 1914.

2. Kahlmeter, G.: Y a-t-il des formes de rheumatisme articulaire et périarticulaire d'une nature réellement allergique? Acta med. Scandinav. **102**:432-443, 1939.

be well for three or four days, until another joint was affected, generally less severely and only for two days. At intervals of about one week she would have a third and a fourth attack lasting only a half or one day. After such a small group or chain of three or four bouts her joints were entirely well for two or three months. Diagnoses of rheumatism, fallen arches and arthritis were made. Treatment included tonsillectomy, physical therapy and shoe correction. In 1924 and 1925 she had only one short run of attacks yearly. During them she could not wear shoes or play the piano. She had no attacks in 1926, but in 1927 the attacks became more extensive and more severe. The fingers, left wrist, shoulders, left knee, ankles and toes were affected. Four or five joints would swell and become painful, tender and stiff for from one to four days; then the process would subside quickly without residual disability. Attacks occurred in October and December of 1927 and in May and twice in July of 1928.

In the four years before the onset of articular symptoms (1916 to 1920) short attacks of hives, which were thought to be due to strawberries and fish, appeared five or six times yearly and involved the eyes, face, ears, abdomen, arms or legs. The hives appeared only occasionally near joints; they generally were located elsewhere. During 1920 and 1921, when her joints were more or less continually affected, she had only three or four attacks of hives lasting one or two days and promptly controlled by epinephrine. Between 1924 and 1926, when articular attacks were *least* frequent, she had the most severe attacks of hives, lasting three or four days and coming four or five times yearly. Although the hives rarely were present when joints were affected, if an articular attack was already in progress the subsequent appearance of hives seemed to aggravate the joints. The joints also were made worse by heat and by menses, but not by changes in weather. The patient and her father, a physician, considered that the hives and the arthritis, since the two conditions rarely occurred coincidentally, were not related or were related only remotely.

The patient's history otherwise and the family history were not significant. She did not have any other allergic manifestations (such as migraine, asthma or hay fever) and had not lost weight despite her illnesses.

Physical Examination.—The physical examination on the patient's admission to the clinic gave essentially negative results except for certain joints. There were swelling and tenderness at the proximal interphalangeal joint of the right third finger; the left knee, which had just recovered from an attack, was normal; the right ankle was slightly swollen, tender and painful on motion; the right fourth toe was definitely swollen, tender and painful. There was no urticaria. The next day several metacarpophalangeal joints were red and a small patch of urticaria was present on the abdomen. No focal infection was discovered.

Laboratory Data.—The urine was normal. The hemoglobin reading was 75 per cent (Dare method), and erythrocytes numbered 4,500,000 and leukocytes 9,400 per cubic millimeter of blood. The flocculation test for syphilis gave negative results. The concentration of uric acid (whole blood) was 4 mg. per hundred cubic centimeters, of calcium (serum) 10.2 mg. and of potassium (serum) 4.4 mg. The sedimentation rate was not estimated in 1928.

Roentgenograms.—Those of the hands and of the right foot showed a normal condition.

Preliminary Diagnosis.—This was recurrent acute arthritis of unknown origin or questionable allergic arthritis. Diagnoses of rheumatoid (chronic infectious, atrophic) arthritis or of recurrent rheumatic fever could not be made because of the absence of residual articular or cardiac pathologic changes after "hundreds" of attacks. Despite the occurrence of repeated short attacks with complete remissions and the involvement of the great toes, a diagnosis of gout was not seriously entertained; gout rarely affects females, especially young females, and tophi or definite hyperuricemia was not present. Furthermore, the clinical pattern of the disease in this case differed materially from that of gout, in that the attacks lasted a shorter time and came much more frequently. Nevertheless, it was decided to note the effects of high and low purine diets and of colchicum.

Subsequent Course.—The patient was given a diet rich in purines; the blood uric acid rose from 4 to 4.3 and 4.7 mg. per hundred cubic centimeters; instead of becoming worse during this time, the involvement of the joints rapidly cleared up. However, a severe attack of hives occurred and lasted three days. In the next few days two or three other attacks of hives were provoked, apparently by sweetbreads but also by other foods. Cutaneous tests with a wide variety of foods, including fish, sweetbreads and strawberries, gave negative results. During the attacks of urticaria the joints remained normal. The urticaria was relieved by epinephrine and colloid baths, but it was neither relieved nor prevented by the use of colchicum. The patient was dismissed with advice to avoid the foods suspected of causing the urticaria. This she did for four months. A month after dismissal she had pain in the joint of one big toe for a few hours, but no urticaria.

Some months later, after she had eaten clams, lobsters and shrimps, a short attack of hives but no arthritis developed. We saw the patient again in 1932; the value for blood uric acid was 3.4 (normal 2 to 4.5) mg. per hundred cubic centimeters. Since 1929 she has taken a normal diet. She has had no further attacks of arthritis. Between 1929 and 1940 she had about six attacks of urticaria. She thought they were due to eating strawberries and fish, but she often had eaten these foods without subsequent hives. The patient now lives in Rochester and has been under repeated observation. Her joints and heart are still entirely normal (February 1942).

Comment on Case 1.—The relationship between the patient's attacks of hives and the arthritis is obscure. The two diseases rarely coincided; but because of the urticaria we suspected, though we could not prove, that the articular reactions also might represent an allergic response. The significance of the fact that the arthritis disappeared when the patient adopted certain dietary restrictions is counterbalanced by the fact that the arthritis did not later reappear after the patient returned to a general diet. A diagnosis of "allergic arthritis," therefore, was considered unproved but allowed to stand for purposes of indexing and further study.

CASE 16 (table 1).—*The case of most severe involvement in this series, with arthritis, para-arthritis, periarthritis.*

This case will be reported in considerable detail, as the involvement was the most severe and the case exhibits best the features of the disease and is illustrated

with several photographs (figs. 1 to 10) which show clearly the transient, yet recurrent nature of the attacks.

A housewife aged 39 was admitted to the clinic Dec. 11, 1936 because of (1) recurrent "rheumatism," with painful swellings of joints almost daily for six years, (2) subcutaneous para-articular swellings, generally near but not over joints, occurring frequently for four years, and (3) small intracutaneous or subcutaneous nodules, appearing frequently at various sites of pressure and elsewhere for three years.

"Rheumatism."—In April 1930 the patient began to have recurrent attacks of swelling, pain, redness and stiffness of various joints; attacks came almost daily, generally lasted only eight to twelve hours, occasionally twenty-four hours, and left the affected site or sites normal until their next involvement. They were so numerous that an almost continuous succession of daily attacks involved some joint or other. While on a summer vacation in 1936 she had, for no known reason, been free of daily attacks for a few days, the only time in six years.

Attacks affected one joint or several joints at a time. Usually the patient was well each day until about noon or early afternoon. Then a joint or joints became swollen, painful and often red. The attack reached its maximal intensity usually about 4 or 5 p. m., receded during the evening and disappeared during the night. With few variations such attacks had occurred day after day for six years, yet the joints each morning were generally entirely normal and no deformity or chronic disability had appeared. Joints involved in the order of frequency were those of the fingers, knees, ankles, elbows, toes, shoulders, spine, wrists and hips. When the shoulders, spinal column and hips were affected there was aching pain but no swelling. Other joints definitely swelled. Some metacarpophalangeal and proximal interphalangeal joints, a knee or an ankle was affected almost daily. The elbows, shoulders, spinal column, wrists and toes shared in the attacks only about once a week; terminal phalangeal joints were involved two or three times monthly and the hips less frequently. Of all regions affected the shoulders became the most painful, but joints of the fingers swelled the most frequently. Often a finger swelled to twice its normal size and the skin became tight. The recurrent swellings of fingers had been so notable for three years that the skin had been stretched, and as the swelling subsided it left the skin markedly wrinkled (fig. 1 *a*). When joints were swollen, articular tenderness was pronounced and there was a "deep ache as though the pain were in the bone." Often joints were sufficiently disabled and painful to force the patient to lie down all afternoon, although she rarely had to undress and go to bed. The more housework she had to do the worse the attacks were; rest moderated but never entirely prevented the attacks. They were worse the week before, and less severe the week after, menses. They were not related to weather, season or any known food. The patient did not have asthma, hay fever, eczema or known sensitivity to any drug or food, but occasionally she had mild headaches. The articular swellings had been unaffected by numerous treatments: various pills, a diet poor in meat and salt, physical therapy, chiropractic treatments and removal of teeth and tonsils.

Fig. 1 (case 16).—(*a*) Dec. 11, 1936, both hands. The skin over the fingers has been stretched by the recurring swellings. When the swellings subsided, the skin was left markedly wrinkled. Nodules may be seen (1) on the mesial aspect of the right index finger; (2) over the proximal phalanx of the left fifth finger, and (3) over the terminal joint of the left third finger. The dorsum of the left hand is slightly swollen. (*b*) Dec. 16, 1936, right hand. The proximal interphalangeal joint of the fourth finger is now swollen.

Subcutaneous Swellings (Para-Arthritis).—During the four years before the patient's admission many of the articular attacks had been accompanied by rather small subcutaneous swellings which lasted one to four days and affected tissues above or lateral to a knee joint, about a malleolus, on the dorsum of a foot, on the extensor surface of an arm, just distal to an elbow

or proximal to a wrist, or over the dorsum of a hand just proximal to one or two metacarpophalangeal joints. Occasionally also one or more finger tips or finger pads (flexor surfaces of the distal phalanges) would swell up in connection with swelling of a proximal interphalangeal or terminal phalangeal joint. These regions of puffiness varied in diameter from that of a dime to that of a silver dollar (7/10 to 1½ inches; 18 to 40 mm.), pitted slightly on pressure, were slightly tender and ached or burned. The finger pads especially would become sensitive for a few hours.

Intracutaneous or Subcutaneous Nodules.—The patient had also noted for three years the occasional appearance

Fig. 2 (case 16).—Dec. 23, 1936. (*a*) The proximal interphalangeal joint of the right fourth finger is no longer swollen; the terminal joints of the fourth and fifth fingers are now swollen. (*b*) Swelling on the flexor surface of the left forearm, proximal to the wrist.

of small subcutaneous or intracutaneous nodules or papules near the elbows, knees or wrists and especially on the fingers. They came rather suddenly, lasted sometimes only a few days, but usually about two to five weeks, and then disappeared completely. The only nodule which had persisted had been on the mesial aspect of the right index finger for about one year (fig. 5). These nodules were usually somewhat tender, more so than the regions of para-articular puffiness. The nodules seemed to bear a relationship to trauma and appeared especially at sites of pressure. A bump would not precipitate one, but a few hours' pressure of an elbow on the arm of a chair or of the head on the back of a chair or of the buttocks on a chair seat would cause one to form. Hence the patient had padded the arms, seats and backs of her chairs. Such nodules appeared near the elbows frequently, on the back of the scalp two or three times a month and on the forehead occasionally.

History.—The patient had scarlet fever in 1911, underwent cholecystostomy for obstructive jaundice in 1923, and suffered from pleurisy, pneumonia and phlebitis of one leg and had tonsillectomy performed in 1933. The family history was irrelevant except that one sister had hay fever, another had migraine and two nephews had hives after eating certain foods.

Physical Examination.—The patient's first examination at the clinic was in the morning, at which time the joints all appeared normal; none were tender or sore. There was slight puffiness, however, over the dorsum of the left hand (fig. 1 *a*). Nine small, firm intracutaneous nodules, one near each olecranon process, and seven scattered over the ventral and dorsal surfaces of the fingers were present (figs. 1 *a*, 3 *a* and 5). These were elevated about 1 to 2 mm. and were about 3 to 8 mm. in diameter. The skin of the fingers was wrinkled, and the subcutaneous tissues of the surfaces of the fingers were loose and seemed atrophic, as if there had been much previous subcutaneous swelling (fig. 1 *a*). General and neurologic examinations otherwise gave negative results.

Laboratory Tests.—A flocculation test for syphilis gave a negative result. Many urinalyses were made, all showing a normal picture. Concentrations of uric acid were: in whole blood 3.1, per hundred cubic centimeters, in plasma 4.4 mg. and in serum 5.0 mg. The value for plasma cholesterol was 175 mg. per hundred cubic centimeters, for lecithin 223 mg., for fatty acids 280 mg. and for total lipids 455 mg. The sedimentation rate was 10 mm. (one hour) before an articular attack and 12 mm. (one hour) during an attack. The hemoglobin reading was 14.5 Gm. per hundred cubic centimeters; erythrocytes numbered 4,300,000 per cubic millimeter of blood and leukocytes 8,400 to 10,000. Several differential leukocyte counts revealed neutrophils 48 to 68 per cent, lymphocytes 25 to 45 per cent, monocytes 1 to 7 per cent, eosinophils 1 to 5 per cent, filamented cells 38 to 56 per cent and nonfilamented cells 8 to 22 per cent. The sedimentation rates and total and differential cell counts did not vary significantly before, during and after an attack of arthritis.

Roentgenograms of the hands (fig. 6), wrists, elbows, knees, ankles, feet and chest were entirely normal. Hemolytic streptococci were readily found in each of three nasopharyngeal cultures. Specific lesions were not produced when they were injected into two rabbits; the animals' joints remained normal. These streptococci when injected into the patient's skin produced only slight reactions. Cutaneous tests with a number of pollens, foods and hairs all gave negative results. The cold allergy test of Horton, Brown and Roth[3] was negative.

Subsequent Observations.—The patient was studied in the hospital for twenty-seven days (Dec. 15, 1936 to Jan. 10, 1937). During this time we observed a series

3. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold with Local and Systemic Manifestations of a Histamine-Like Character: Its Amenability to Treatment, J. A. M. A. **107**:1263-1268 (Oct. 17) 1936.

of short, acute attacks of arthritis and the appearance on several occasions of swellings of para-articular soft tissues and on four occasions of nodules (fig. 1 *b* and figs. 2 to 5). At no time was fever present.

Arthritis.—During the twenty-seven days the patient had fifteen attacks of arthritis, chiefly in joints of fingers. In nine attacks only joints of fingers (one or more) were affected, and in five, joints other than of fingers. In only one were joints of fingers and other phalangeal joints (not finger pads). Other regions involved during these twenty-seven days were the left ankle twice, the left great toe (whole toe) twice and the left knee, left hip, right shoulder and back once each. The same joint was rarely affected on two successive days; generally three or more days elapsed before a given joint was involved again.

The patient's joints generally appeared normal each morning. Usually an attack began between noon and

Fig. 3 (case 16).—Dec. 28, 1936. (*a*) The pads of the right second and third and of the left third, fourth and fifth fingers are swollen; note the scattered small subcutaneous nodules. (*b*) The terminal joints of the right fourth and fifth fingers are no longer swollen; compare with figure 2 *a*.

joints simultaneously attacked. In six of the ten attacks affecting joints of fingers only one joint was affected; in three attacks, two, and in one attack, three. Proximal interphalangeal joints were affected much oftener than other joints of the hands (fig. 7). The attack of Dec. 23, 1936 involved no proximal interphalangeal joint but affected a metacarpophalangeal joint and was the only attack which involved terminal

3 p. m., reached its maximal intensity of swelling and pain in about four or five hours and was practically gone the next morning. On the morning after the attack there was generally no objective or subjective evidence of the previous day's attack except occasionally slight tenderness on firm pressure or a faint residual puffiness at the site of the last attack. Repeatedly within about twenty-four to thirty-six hours the joints

were fully restored to normal function and also, as the photographs (figs. 1 to 4) show, to normal appearance. The amounts of articular swelling present before 4 p. m. were apparent to the naked eye and to the palpating finger but were often not such as could be readily reproduced in photographs; that amount of swelling usually did not appear until between 5 and 9 p. m. On rare occasions an attack began between 9 and 11 a. m. or after the evening meal.

Articular swellings were generally of grade 2 on a grading basis of 1 to 4, rarely less and occasionally more. For example, during one attack the circumference of the proximal interphalangeal joint of the right fourth finger increased from 5.7 to 7.2 cm. and that of the same joint on the right index finger from 6.5 to 7.2 cm. Pain was definite and annoying, generally graded 2 (moderate or notable but not severe). Tenderness of grade 2 was usually present, redness of grade 1 to 2 and stiffness of grade 1 + to 2.

intercellular and intracellular edema in the epidermis but no other noteworthy changes.

Para-articular Swellings (Para-Arthritis).—These occurred on each of fourteen days while the patient was in the hospital; their diameters (0.7 to 1.2 inches; 1.8 to 3 cm.) varied from the size of a dime to that of a 50 cent piece. They affected various parts of the hands oftener than other sites. They appeared on the hands alone on six days, on the hands and elsewhere on six, and elsewhere but not on the hands on two. A favorite site was the dorsum of the right hand proximal to, rather than over, the metacarpophalangeal joints. As indicated in figure 7, three such regions on the two hands were repeatedly affected, but even when the same site was affected on two successive days there was an interval when the swellings disappeared for a few hours. These regions of swelling pitted slightly, were slightly reddened, were tender and ached or burned. Especially notable were the swellings which involved

Fig. 4 (case 16).—Jan. 6, 1937. The terminal joints of the right fourth and fifth fingers are still normal; the proximal interphalangeal joints of the left second and third fingers are swollen and cannot be fully extended.

On twelve of the twenty-seven days there were no attacks of arthritis, possibly as the result of treatment, which will be discussed later.

On Jan. 7, 1937, biopsy of the skin, articular capsule and surrounding tissues at the proximal interphalangeal joint of the left index finger was performed during an attack in this joint that had begun about twenty to twenty-four hours before.

When the subcutaneous tissues were exposed some milky fluid ran out, and when the joint was opened cheesy bits of coagulated material came out. The histologic reactions were those of a nonspecific acute inflammation. The coagulated exudate within the joint consisted of a loose fibrin network, enmeshing innumerable leukocytes, mainly polymorphonuclears; in other words, it was a fibrinopurulent exudate (fig. 8). The synovial membrane revealed acute inflammation with widespread exudation of polymorphonuclear leukocytes and notable inflammatory thickening of synovial villi (fig. 9 *a* and *b*). Eosinophils were not present in significant numbers. No urate crystals were found in sections stained by Galantha's silver stain. Sections of the skin overlying the joint showed the presence of

several finger pads on December 28, again on December 29 and on January 8 (fig. 3 *a*). The pads ballooned out so that the skin over them was taut. The pads were only slightly reddened but were tender; they burned and throbbed, and their skin temperatures (with the Constantin and copper galvanometer) were 4 to 6 C. (7.2 to 10.8 F.) higher than those of adjacent unaffected finger pads. The swellings extended up to and occasionally proximal to the skin crease of the corresponding terminal phalangeal joint, but the joints themselves seemed to be uninflamed although somewhat stiffened by the adjacent swelling.

Other sites of these para-articular swellings were the flexor and extensor surfaces just proximal to the wrists (fig. 2 *b*), the flexor surface of the metacarpophalangeal joint of the left third finger, the arms just below the olecranon processes, the lateral aspect of the right knee, above the left patella, about the left external malleolus and over the dorsum of either foot. Often these various swellings on the hands and elsewhere, though distinct, were not gross enough to show in photographs except as a slight blurring of tissues or

smoothing out of contours and wrinkles, but some of our photographs show them more clearly.

Nodules.—The sites of the nine intracutaneous nodules present on the patient's admission have been mentioned. During the twenty-seven days of observation four new nodules were noted, two on the dorsum of the right wrist, one in the occipital region and one over the

Fig. 5 (case 16).—Jan. 6, 1937. The nodule visible on the right index finger has been present for a year. The nodule on the thumb has been present for a few hours.

proximal interphalangeal joint of the right thumb, which was visible only a few days (fig. 5). The older nodules were for the most part essentially painless, but several of them became sore during one of the articular attacks. One of the original nodules (left index finger) was incised for biopsy December 11. Microscopic examination revealed a nonspecific inflammatory reaction resembling that in the articular capsule but less acute (fig. 10 *a* and *b*). The cellular elements of the fibrous tissue were proliferating actively; there were occasional mitotic figures among the young fibroblasts. The tissue was vascular, and occasional polymorphonuclear leukocytes, lymphocytes and plasma cells were present about the small blood vessels. In many of the blood vessels the endothelial cells were tall and swollen.

Treatment.—During the early stages of the attack of Dec. 22, 1936, involving finger joints, subcutaneous injections of 1:1,000 solution of epinephrine hydrochloride, 10 and 8 minims (0.6 and 0.48 cc.), given thirty minutes apart, failed to modify the usual progress of the attack. The administration of ephedrine, 7 capsules daily (each ⅜ grain; 0.024 Gm.) on December 24 and 25, did not apparently influence the attacks. Amphetamine sulfate, 20 mg. twice a day, was given December 26 and 27. On December 26 the left great toe swelled and soft tissue swellings appeared in several other regions, but on December 27 the patient was entirely free of arthritis or swellings, her first "well" day in six months. Intravenous injections of triple typhoid vaccine (25,000,000 and 50,000,000 bacilli) were given December 29 and 31, with satisfactory general reactions, and on January 1 daily injections of histamine for desensitization were begun. From December 27 to January 3 inclusive the patient's joints were free from attacks, although para-articular swellings had occurred December 28 and 29. No articular attacks occurred January 5, 8 and 9, although para-articular swellings occurred January 8 and 9. Whether this unusual freedom from articular attacks was due to the reactions to typhoid vaccine remains problematic. After dismissal the patient was asked to submit again to reactions to typhoid vaccine, but has relied on injections of histamine at home.

On January 8, after para-articular swellings had affected several finger pads and the dorsum of the right hand, 5 cc. of a 1 per cent solution of procaine hydrochloride was injected into the sixth, seventh and eighth cervicodorsal nerves on the right side. Within five minutes Horner's syndrome was produced on the right side. Thereafter the cutaneous temperature of the right forearm and hand increased, with an apparent reduction in the pain and burning, and probably also some reduction in the size of the swellings.

The factor of rest seemed to be important. The patient insisted that her attacks in the hospital, despite their frequency, were not as severe as those she had while working at home. Therefore, on several days we prescribed three or four hours of rather strenuous occupational therapy and three or four miles of walking; on these days her attacks were somewhat more severe. Because of this rest factor we are unwilling to make any final conclusions as to the value of the treatments used in the hospital.

The patient was dismissed to continue further treatment at her home: injections of histamine, oral adminis-

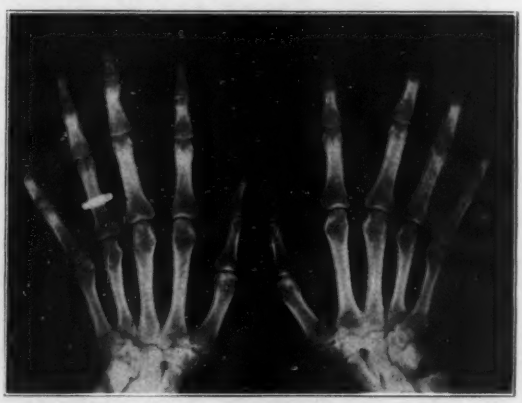

Fig. 6 (case 16).—Dec. 19, 1936. The roentgenogram of the hands (taken after removal of biopsy specimen from the left index finger) is normal despite the fact that the patient has experienced hundreds of episodes of arthritis during the preceding six years.

tration of histaminase and injections of an autogenous hemolytic streptococcus vaccine. She obtained no relief from further use of amphetamine or histaminase. Injections of histamine were given through April 1937; the patient's physician was of the opinion that the injections

did not help much, but the patient herself repeatedly wrote us that she was much benefited thereby and that although she was still having frequent attacks she occasionally had three or four days without attacks. When use of histamine was stopped, the patient's attacks became more severe; therefore her physician (March 1938) reinstituted such therapy.

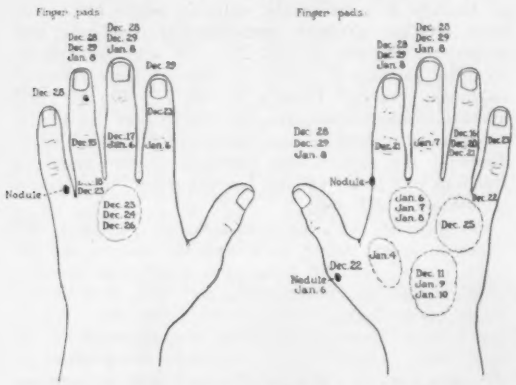

Fig. 7 (case 16).—Sites involved by attacks which occurred in the hands while the patient was under observation at the clinic (Dec. 11, 1936 to Jan. 10, 1937).

Follow-up Study in Case 16.—In April 1940, the patient wrote that she was still having about three or four attacks of arthritis every week; the attacks came on in the afternoon and disappeared entirely at night. There was still no chronic articular deformity; certain cutaneous nodules persisted. The attacks still seemed to be precipitated or aggravated by work, and perhaps also by changes in weather, but the attacks were less severe and she felt "much better" since having had the injections of histamine.

CASE 20 (table 1).—*The case of a noted orthopedist with multiple articular and para-articular attacks.*

A noted orthopedic surgeon, aged 73, was admitted to the clinic Jan. 31, 1938, because of "rheumatism" of thirteen years' duration. In 1924, after he played golf, his right shoulder suddenly became painful for two weeks and then cleared up. Ever since then he has had recurrent attacks of acute arthritis (in various joints) "time and again," according to his estimate five hundred or six hundred attacks in thirteen years. Despite their frequency, all attacks disappeared completely, leaving no residual disability. He stated the belief that his joints had been involved as follows: elbow joints, each about seventy-five times, left knee, wrists and hands, each about fifty; hips, about twenty-five; right knee and sternoclavicular joints, each about twenty, and shoulders, each about four. In the hands various proximal interphalangeal and metacarpophalangeal joints were attacked but never the terminal phalangeal joints. The spinal column and feet also had escaped involvement. In any one attack, generally only one, but occasionally two joints, never more, were affected in rapid succession.

The first attack, which was the longest, lasted two weeks; a few lasted two to three days, but most of them lasted only from three to twenty-four hours. They were all afebrile. At first the attacks came only about once in three or four months, but recently they had come much oftener. Intervals between recent attacks were: shortest, one day; longest, one month; usual period, eight to ten days. During each of the past two years, therefore, the patient had had about fifty attacks.

A typical attack occurred thus: Going to bed well, the patient often woke up in an attack or an attack would develop suddenly in the morning. Many attacks, however, occurred at other hours. Attacks developed "almost instantaneously," progressed rapidly, lasted from three hours to three days and disappeared completely. Articular disability disappeared between episodes. Outstanding features were periarticular swelling and pain. Swelling was often severe enough so that periarticular tissues became tense, but the skin was not reddened. As an orthopedist the patient had concluded that the swelling was periarticular, not due to intra-articular effusion, but he could not identify his disease with any type of arthritis with which he was familiar. Many attacks were only moderately painful and were relieved by 5 grains (0.3 Gm.) of acetylsalicylic acid, but often pain was so intense that he was forced to remain in bed. Earlier attacks had been less frequent but in general more severe, so that hospitalization was required every three or four months; recent attacks had been more frequent but less severe.

Attacks bore no relationship to season or to weather. Precipitating factors seemed to be slight trauma or fatigue and perhaps also ingestion of chicken. There was no evidence of familial or personal allergy—no asthma, hay fever, eczema, urticaria, migraine or

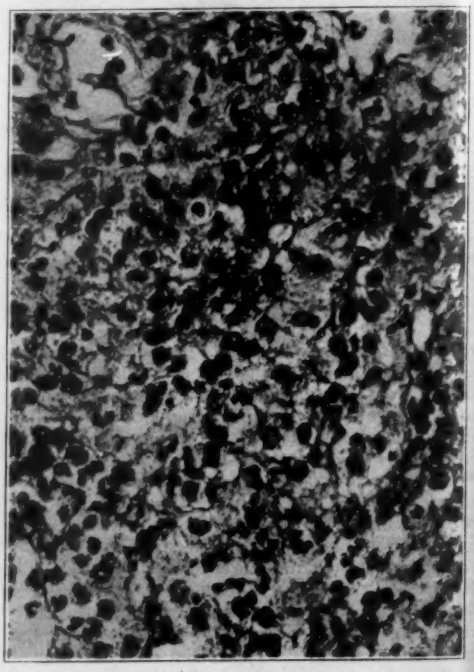

Fig. 8 (case 16).—Character of the fibrinopurulent exudate found within a joint during an acute attack (× 500).

sensitivity to drugs. Prior to his admission to the clinic the patient had had numerous cutaneous tests with various foods and bacteria, some of which had produced positive reactions, but a bacterial vaccine based on these reactions had caused severe general reactions and had been discarded. The fairly pro-

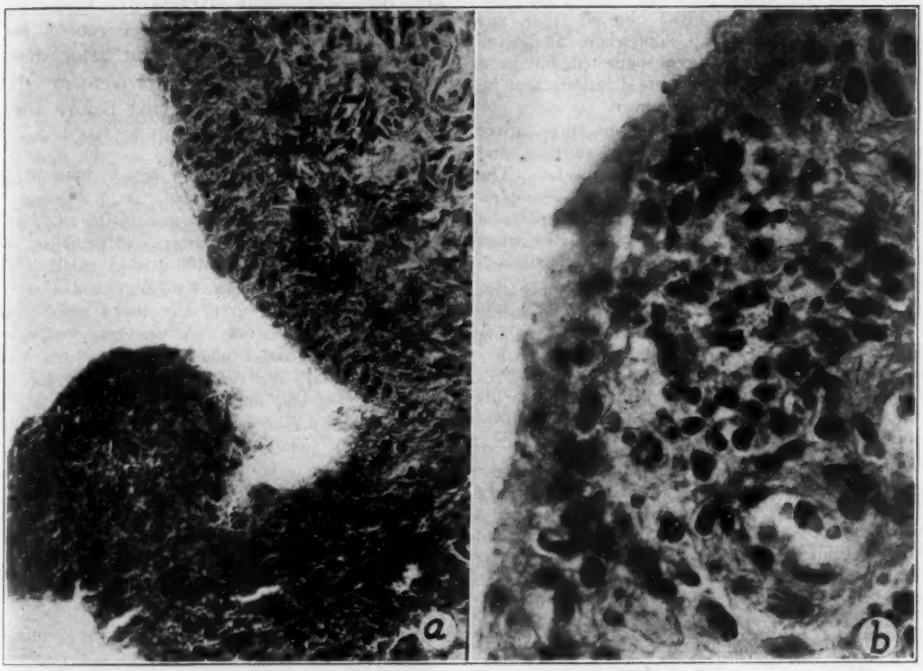

Fig. 9 (case 16).—Acute inflammatory reaction present in the synovial membrane during an acute attack. There are widespread exudation of polymorphonuclear leukocytes and notable thickening of the synovial villi. (*a*, × 310; *b*, × 700.)

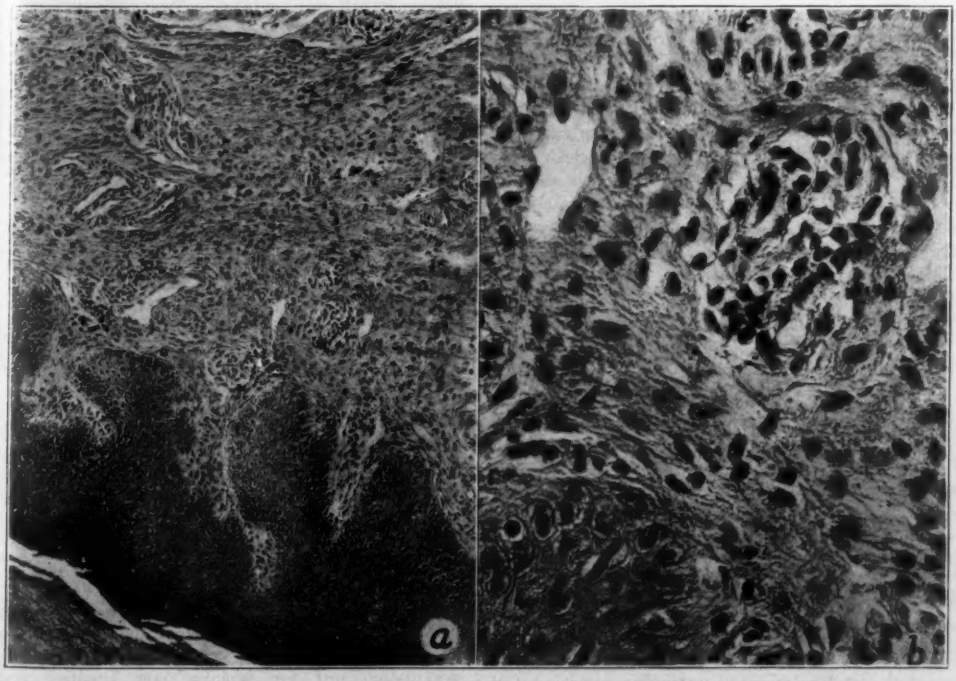

Fig. 10 (case 16).—The nonspecific chronic inflammatory reaction present in a subcutaneous nodule. The fibroblasts are proliferating; the tissue is vascular, and occasional inflammatory cells are seen about small vessels. (*a*, × 100; *b*, × 400.)

longed use of a diet which contained none of the supposedly offending foods had given him no relief, nor had injections of epinephrine. Somewhere along the line a diagnosis of gout had been suggested, but as a physician he thought so little of this diagnosis that he never instituted the appropriate regimen.

In addition to the articular reactions, the patient had had numerous episodes of brawny swelling and induration of each forearm but nowhere else. The affected region became firm and tender for a few days. For two years he had had some precordial pain on exertion. His past history included scarlet fever when he was a child, tonsillectomy in 1920 and influenza.

Physical Examination.—This gave essentially negative results. Objectively all joints were normal, and roentgenograms of an elbow, knee and wrist revealed nothing significant. Other roentgenograms showed slight hypertrophic arthritis of the thumb and the right hip. This was considered to be the coincidental osteoarthritis usual in a man of his age and entirely unrelated to his chief articular disease. No infected foci were found.

Laboratory Data.—The patient had mild anemia; the concentration of hemoglobin was 12.9 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 4,010,000 per cubic millimeter of blood. Total and differential leukocyte counts and values for blood calcium, phosphatase and cholesterol esters were normal. The value for uric acid in the blood was 4.8 mg. per hundred cubic centimeters, that for serum phosphorus 2.6 mg. (slightly low) and that for plasma cholesterol 303 mg. (slightly high). The sedimentation rate was 54 mm. per hour during the swelling on the arm noted hereafter. Culture of material from the nasopharynx revealed green-producing streptococci, which when injected intravenously into rabbits produced hemorrhagic lesions in muscles and periarticular fascia and a hemorrhagic turbid exudate in certain joints. Most of the cutaneous tests made with various foods, including that with chicken, gave negative results. Reactions were slightly positive to whole wheat, beef, cocoa, coffee and tea. While in Rochester the patient ate a duck dinner; forty-eight hours later a painless, colorless, nontender swelling developed over the left forearm near the wrist but disappeared entirely in a few hours; joints were not affected.

Diagnosis.—As in case 1, a tentative diagnosis of "allergic arthritis" was made, on Feb. 4, 1938, largely for indexing purposes; a diagnosis of coronary sclerosis was also made. The patient was dismissed to note the effect of ephedrine, histamine and histaminase, and to keep a food diary.

Subsequent Course.—Two weeks later, before any treatment had been begun, the patient noted transient swelling of a metacarpophalangeal joint which lasted two days. On March 5, 1938, he wrote that he had had no further trouble: "I don't know when I have been so long without an attack before." He began to take injections of an autogenous streptococcus vaccine, but on Aug. 11, 1938 he died of coronary disease.

Comment on Case 20.—In this, as in the previous cases, a diagnosis of rheumatoid (chronic infectious, atrophic) arthritis or gout seemed untenable. The history and clinical findings suggested the presence of articular reactions of an allergic nature, but this could not be proved, nor could the antigen be definitely identified. The nasopharyngeal streptococci may or may not have been significant. The reason for the patient's apparent improvement after dismissal was not obvious, as the improvement, that is, a respite from attacks, started before the prescribed treatment was begun.

CASE 27 (table 1).—*Case in which articular biopsy was made as an attack subsided.*

A housewife aged 41 years came to the clinic Jan. 23, 1939, because of recurring attacks of arthritis for two years. She had had about 100 attacks in all; each one lasted a few hours or a few days and then disappeared. During the first year the attacks generally lasted less than a week. A year previously several joints of both hands suddenly swelled and were as "sore as a boil" for two weeks. She could not do housework but did not have fever. Then the hands promptly returned to normal. The longest attack was three weeks, and some of her most painful attacks lasted only a few hours. Sometimes she had two or three attacks a week and sometimes none for three weeks; the average was about one weekly.

In an attack generally only one joint was affected, a finger joint, wrist, elbow, shoulder, knee or toe; occasionally several joints were involved, but 90 per cent of her attacks affected some part of a hand. Attacks came suddenly at any hour, but more often between 3 and 6 p. m. or in the middle of the night. One hour she would be "feeling grand"; the next hour she would be miserable. Swelling and pain reached their maximum within two or three hours. An affected joint became slightly red and sufficiently swollen to iron out wrinkles in the skin and make it shiny. Mild attacks consisted of articular pain without swelling. The pain was throbbing or knifelike, was equally severe day and night and often kept her awake. Disability was such that if a knee was involved she had to go to bed; an affected hand prevented housework.

The patient knew of no cause for the attacks. Attacks were unrelated to work or menses, but were less severe in summer. Despite her hundred attacks she had not lost weight and her appetite was good. There was no personal or familial history of allergic reactions. The patient had seen several physicians; no definite diagnosis had been made. Tonsillectomy had not stopped the attacks.

Physical Examination.—On admission the patient was in an attack (fig. 11). The proximal interphalangeal joint of the left second (index) finger was swollen and slightly stiff. All other joints appeared normal. The finger remained affected for several days. The only infected focus found was a tooth.

Laboratory Data.—The sedimentation rate was 8 mm. in one hour. The concentration of uric acid was 2.7 mg. per hundred cubic centimeters of blood; of cholesterol 315 mg., of cholesterol esters 277 mg., of lecithin 260 mg., of fatty acids 569 mg. and of total lipids 884 mg. per hundred cubic centimeters of plasma. That of hemoglobin was 13.5 Gm. per hundred cubic centimeters of blood. Total and differential leukocyte counts were normal; 2 to 3 per cent of the leukocytes were eosinophils and 17.5 per cent nonfilamented cells. A flocculation test for syphilis gave negative results. Roentgenograms of the hands, elbows and knees and the right foot were normal. An agglutination test for Brucella abortus and the cold allergy test gave negative

results. Cutaneous reactions to tests with many antigens were all negative except for a reaction of grade 2 to corn and to cocoa.

Subsequent Course.—On February 6 the proximal interphalangeal joint of the left index finger was incised for biopsy; the attack in that joint was subsiding. The joint contained an increased amount of normal-looking fluid, and its capsule was thickened. Cultures of material from the joint and of the fluid on brain broth and brain agar revealed no organisms.

Microscopic examination of tissue from the capsule (fig. 12 *a* and *b*) revealed actively proliferating fibrous tissue; with many young fibroblasts, a few inflammatory cells, including polymorphonuclear leukocytes, were scattered about small vessels.

The patient was fed large amounts of foods which she suspected might be causing the attacks: corn, cocoa, macaroni, potatoes, rice, and so forth. No attack was precipitated, and on Feb. 9, 1939 she felt fine; there was no pain anywhere and she stated that she "could run a race today."

Fig. 11 (case 27).—The proximal interphalangeal joint of the left index finger is slightly swollen and stiff. This cleared completely in a few days.

Histamine desensitization was begun. During the patient's stay at the clinic no other attack developed. She was dismissed Feb. 13, 1939, with instructions to continue the histamine therapy and to have the infected tooth removed. These measures did not give permanent relief, and she still suffers from the recurrent attacks. However, she has not lost weight and does not have articular residues.

CASE 30 (table 1).—*Case in which biopsy of wrist was made during an acute attack.*

A farmer aged 35 came to the clinic June 22, 1939, because of many attacks of "rheumatism" over a period of six years. In 1933 his knees became painful for several weeks; then the pain disappeared. About eight months later he began to have recurring short attacks of acute arthritis, and he has had about one hundred and fifty attacks in the past five years. Between attacks his joints become entirely normal. The attacks appeared any time of day or night, but especially at night, often around midnight. He estimated that he had had seventy-five attacks in the hands, twenty-five or thirty in a shoulder, fifteen each in an elbow or ankle and about fifteen more attacks involving a knee, a hip or the neck. The large toe joints were never affected, nor had the patient ever had olecranon bursitis or renal colic. Usually only one joint was affected in an attack, occasionally three joints were involved successively, one being attacked as another joint cleared up.

A joint began to ache and in about six or eight hours became painful, swollen, red and tender. Pain was so severe that for the next one or two days he could not work or sleep. At night the severe pain forced him to get out of bed and walk about or use hot or cold applications to get relief. During an attack he could not eat with an affected hand, could not dress or shave, and so forth, but had to carry the part in a sling. The swelling, pain and redness usually remained for two or three days and then slowly "disappeared 100 per cent, leaving the joint as good as ever." The shortest attack lasted one day; the longest, one week. He had never been aware of any fever with the attacks. They bore no apparent relation to season, weather or food. The patient thought they were sometimes precipitated by overwork and by getting his feet cold and wet. There was no family or personal history of allergic reactions.

Physical Examination.—This gave essentially negative results. The joints were entirely normal. No infected foci were found.

Laboratory Data.—A flocculation test for syphilis gave negative results. Roentgenograms of the elbows, knees, hands and wrists were normal. The hemoglobin value and the total and differential leukocyte counts were essentially normal: 1 and 1.5 per cent eosinophils and 6 per cent nonfilamented cells. The sedimentation rate was 25 mm. in one hour. The concentration of uric acid (aerobic technic) in whole blood was 3.9 mg. per hundred cubic centimeters and in serum 5.2 mg.; of serum calcium 9.5 mg. and of serum phosphorus 3.1 mg.; of plasma cholesterol 219 mg., of cholesterol esters 144 mg., of lecithin 203 mg., of fatty acids 379 mg. and of total fats 598 mg. Many intracutaneous tests made with various antigens gave negative results; cutaneous reactions to whole wheat, oats, corn, rice and cocoa were slightly positive.

Subsequent Course.—At each of five meals the patient had generous amounts of cocoa and whole wheat bread; no attack was produced. Between July 5 and 9, 1939, he ate corn and rice at each meal. On the afternoon of July 9 his left wrist began to throb and ache. That night and the next morning it was slightly swollen, tender and stiff. The wrist was incised. The tendon sheaths of the extensor muscles of the thumb and of the extensor carpi radialis muscle were found to be filled with a murky-looking fluid. In view of the tendonitis, the wrist joint was not opened. Cultures of fluid on brain broth and blood agar remained sterile. Histologic examination of sections from the tendovaginal sheaths revealed nonspecific inflammation. Lymphocytes and a few polymorphonuclears were present about the small vessels and scattered throughout the fibrous fatty tissue (fig. 13).

Treatment.—Histamine desensitization was begun, and the patient was dismissed July 19, 1939, to continue treatment at home.

Follow-Up Study.—In September 1939 the patient wrote that he felt 50 per cent better; he thought perhaps this was due to the injections of histamine. He was still having repeated attacks in various joints, but they were not so severe. He had been unable to connect his attacks with any food eaten. In April 1940 the patient was still having painful attacks in the hips, knees or wrists with severe swelling, which lasted generally three

or four days, occasionally a week. He had had about six attacks since dismissal from the clinic; between attacks the joints still became normal.

Comment on Case 30.—Although we may have precipitated an attack by giving the patient corn and rice, the patient's subsequent observations on food indicate that this was a spontaneous, not an induced, attack. The character and pattern of attacks also suggested that allergic reactions of some sort were repeatedly affecting articular and periarticular (tendinous) tissues, but we were unable to prove that the condition was allergic. Results with histamine were equivocal.

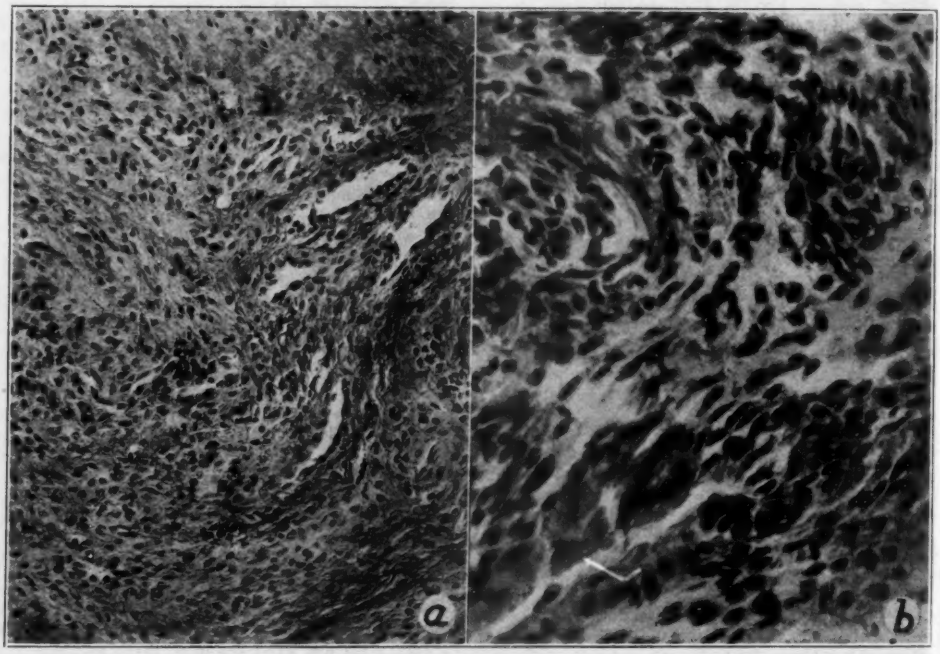

Fig. 12 (case 27).—Character of the inflammatory reaction present in the tissues from the capsule of the swollen joint illustrated in figure 11. Fibroblasts are proliferating actively. A few inflammatory cells, including polymorphonuclear leukocytes, are scattered about small vessels. This attack was subsiding clinically at the time the biopsy specimen was taken. (*a*, × 170; *b*, × 700.)

CASE 34 (table 1).—*Case in which articular biopsy was made between attacks.*

A man 33 years of age came to the clinic Nov. 21, 1939, because of recurrent "joint pains" for ten years. In 1929 the proximal interphalangeal joint of the right third finger suddenly swelled and became red and tender. Having played baseball that day, he attributed the swelling to possible trauma, although he recalled no specific injury. The joint recovered entirely in two days, but every one or two months since then he had had a short attack of acute arthritis involving certain joints, but only one joint at a time. The attacks usually lasted twenty-four to forty-eight hours and then disappeared entirely. As a rule he has had six to eight attacks yearly, but in 1935 he had twenty attacks. He estimated that he had had from eighty to a hundred attacks within ten years: about fifty in a proximal interphalangeal joint of a finger, fifteen or more in the left knee, eight to ten in the right knee and in a metacarpophalangeal joint, five or six in a terminal phalangeal joint of a finger and three in the left wrist. The feet had been affected on only one occasion, when after playing golf once his heel hurt so that he had to walk on the toes of that foot for a day. There was no swelling. It is possible that this single attack in a foot was not similar to the attacks elsewhere.

The attacks usually started in the afternoon. First the joint became sore; then within a few hours it became swollen, red and tender. Usually a painful red region the size of a dime (1 to 2 cm.) appeared near the joint. The joint ached and throbbed; pain and disability were notable but not sufficient to require narcotics or to put the patient to bed. If a knee was affected, he limped; if a finger was involved, he could not type. The length of the attack varied; the shortest, in a finger, lasted twelve hours; the longest, in a knee, lasted four or five days. The time between attacks generally was four to eight weeks, occasionally four months, and on certain occasions the patient had had a short chain of two (never more) consecutive attacks, a metacarpophalangeal joint being affected one day and a midphalangeal joint the next day.

On Oct. 20, 1929, a month before his admission, the patient struck his left knee lightly against a knob in his automobile; the next day he noted a small red sore spot at the left knee near the head of the fibula; the knee became swollen, warm, red, tender and painful for two days; for a few hours thereafter it was less painful and the patient drove a car 300 miles (482 kilometers). This made the knee sore again for a few hours. The attack rapidly disappeared, and the knee

recovered fully within twenty-four hours. Ten days before admission the patient's left wrist became stiff and sore; a small, firm, freely movable nodule appeared "just beneath the skin" but disappeared within six days. Ten or twelve times a red sore spot, "the size of a dime," has appeared on the palm of either hand; unaccompanied by swelling, it remained sore for a few

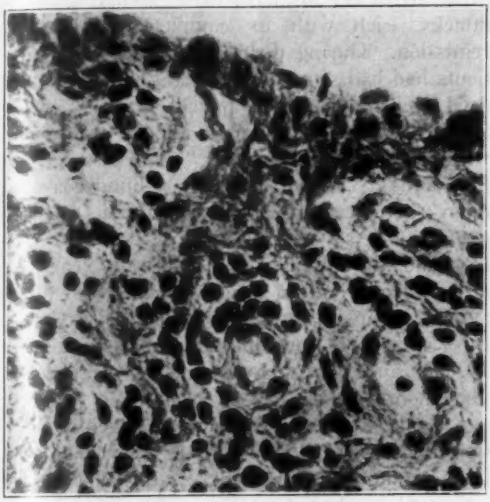

Fig. 13 (case 30).—Histologic appearance of tissue from an inflamed tendovaginal sheath. Nonspecific inflammation with lymphocytes and a few polymorphonuclear leukocytes is present about blood vessels and scattered through the fibrous fatty tissue (× 600.)

hours and then disappeared. They seemed to bear no time relationship to the articular attacks. On six or eight occasions a finger tip became sore and red for twenty-four to thirty-six hours.

Throughout the patient's illness no constitutional reaction, fever, anemia or loss of weight had been noted, and despite the scores of attacks the joints regained their normal appearance and full function.

Precipitating factors appeared to be slight trauma on the occasions noted and possibly foods; the patient suspected that onions and potato salad might have precipitated attacks, but attacks had persisted when he avoided these foods. Numerous cutaneous tests with foods had all given negative results. There was no personal or familial evidence of allergy, hay fever, asthma, hives or migraine. Season and weather did not influence the attacks. Most of the attacks appeared without obvious cause.

Past treatment had included alveolectomies, tonsillectomy, hot applications and various medicines, without relief. The joints had been too painful to permit massage. In August 1938 the patient took 350 grains (22 Gm.) of sulfanilamide within five or six days, but the next attack came after the usual interval.

Physical Examination.—On the patient's admission physical examination gave essentially negative results. The appearance and function of the joints were normal, and no cardiac lesion or focal infection was found.

Laboratory Data.—A flocculation test for syphilis gave negative results. The urine, hemoglobin content and total blood cell and differential counts (eosinophils 2 per cent) were normal. The concentration of uric acid (aerobic technic) was 4.3 mg. per hundred cubic centimeters in whole blood and 5.4 mg. in serum. The concentration of serum calcium was 10.1 mg. per hundred cubic centimeters; of serum phosphorus, 2.7 mg.; of plasma cholesterol, 252 mg.; of cholesterol esters, 174 mg.; of lecithin, 238 mg.; of fatty acids, 312 mg., and of total lipids, 564 mg. The sedimentation rate on Nov. 22, 1939 was 6 mm. in one hour; on November 30, during a mild attack, 30 mm. Cutaneous tests with a large number of foods, pollens and other antigens and the cold allergy test all gave negative results except for a cutaneous reaction of grade 2 to salmon.

Subsequent Course.—We attempted to provoke an attack by the use, on separate occasions, of 0.8 mg. of histamine, given subcutaneously, 50,000,000 typhoid bacilli, given intravenously, and ergotamine tartrate, 0.5 cc. given twice on one day and 1 cc. twice on the next day, but no attack occurred. On Nov. 26 and 27, 1939 the patient received a general diet plus large amounts of onions, potatoes and potato salad. No attack occurred on these days. On November 28 a spot (2 by 2 cm. in diameter) over the left thenar eminence was red and slightly sore, and the internal malleolus of the right ankle became slightly tender and slightly red. These changes lasted for seventy-two hours. They were not aggravated by a subcutaneous injection of histamine. The patient then was given a diet rich in purines and fats for five days. No attack was provoked by this or by two meals rich in salmon. The uric acid content was 3.4 mg. per hundred cubic centimeters of blood before the high purine diet and 3.9 mg. after five days of the diet.

On Nov. 24, 1939, during a remission of the disease, the left knee was incised for biopsy, a piece of synovial membrane and muscle being removed. The joint cavity, cartilages and so forth were carefully inspected grossly and appeared entirely normal. Histologic examination revealed the synovial tissue and muscle to be normal (fig. 14), despite the fact that there had been at least fifteen attacks in this knee. Cultures of the removed

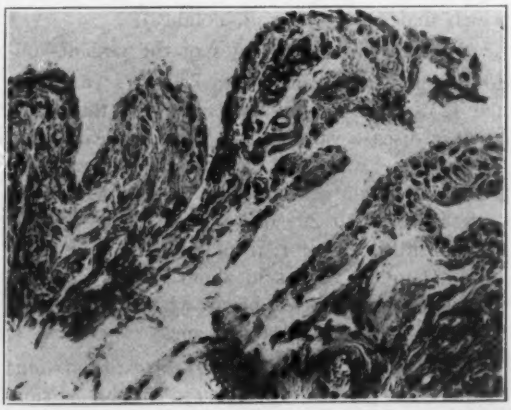

Fig. 14 (case 34).—Normal synovial tissue from the knee. The biopsy specimen was obtained during a remission after at least fifteen attacks in this knee (× 150).

pieces of synovial membrane and muscle on brain broth were negative.

Follow-Up Study.—The patient was dismissed Dec. 18, 1939, to be under the care of his physician at home. We suggested that a food diary be kept and that the effects of ephedrine, ergotamine, histamine desensitization, histaminase, typhoid vaccine, Rosenow's arthro-

tropic streptococcus vaccine and antigout therapy be investigated further. In a letter of April 1940, the patient wrote that he had had no treatment since dismissal and had had three mild attacks. Each had lasted six to twenty-four hours; the joints then recovered completely.

ANALYSIS OF CLINICAL MATERIAL

Data on the frequency, duration and outcome of the acute attacks in all 34 cases encountered in eleven years (1928 to 1939) are presented in table 1.

Relative Incidence of the Disease.—After case 1 was noted by one of us (P. S. H.) in 1928, the disease was not seen (or recognized) until 1931 and 1932, when 5 and 3 cases respectively were observed. None were encountered between 1933 and 1935, but since 1936 from 3 to 9 typical cases have been observed yearly. The relative incidence of this disease according to its present rate of recognition at the Mayo Clinic is, therefore, about 5 or 6 cases in about 4,000 to 4,500 cases of "rheumatism" (articular and muscular diseases of all types) observed yearly by the clinic's consultants on diseases of joints. Thus the condition seems rather rare, but the rate of recognition will probably increase somewhat.[4]

Sex Incidence.—The incidence was relatively equal in each sex (15 males to 19 females); this is a striking contrast to the sex incidence either of rheumatoid arthritis (among patients with which females preponderate) or of gout (with which males preponderate notably).

Age Incidence.—The ages of the patients on admission varied from 21 to 73 years (average age 42). The ages of the patients at the onset of their disease varied from 13 to 68 years; the average age was 34.9 years. The disease of 2 patients began at the age of 13 and 19 years; of 8, from 20 to 29; of 15, from 30 to 39; of 6, from 40 to 49; of 1, from 50 to 59, and of 2, from 60 to 69. Thus in about 70 per cent of the 34 cases the disease began when the patients were from 20 to 39 years of age.

Duration of the Disease Prior to Admission to the Clinic; Total Number of Attacks.—Prior to admission to the Mayo Clinic the patients had had their disease for from four months to twenty-five years. The disease had been present twenty-one to twenty-five years in 2 cases, sixteen to twenty years in 2, eleven to fifteen years in 4, six to ten years in 11, one to five years in 10, less than one year in 5 (but there had already been ten to one hundred and thirty attacks in each of these 5 cases). The 34 patients had had their disease for a total of about two hundred and forty-two years (average seven and two-tenths years).

The striking feature of the disease was the great frequency of irregularly recurring short attacks, each with its complete symptomatic remission. During their illness most of the patients had had scores and several had had "hundreds" of attacks. One patient (case 5), when asked to estimate how many attacks he had had within seven years, replied, "hundreds, perhaps thousands!" Others replied, "hundreds—too many to remember" or "too numerous even to guess at." As stated, even the few patients who had had the disease less than one year had already had from ten to one hundred and thirty attacks. Thus in case 26 there had been twenty-three attacks in four months; in cases 21 and 29, ten and thirty-two attacks respectively in nine months, and in cases 15 and 19, fifty and one hundred and thirty attacks in eleven months. Omitting cases 1, 4, 5 and 16, in which there had been unnumbered hundreds of attacks, the total estimated number of attacks in the remaining 30 cases was from 4,930 to 5,320. Thus the average frequency was, by the smallest reckoning, about one hundred and sixty-four attacks per patient during an average of about seven years of disease, that is, an average of about twenty-three attacks each year. Adding the 4 cases in which there had been "hundreds" of attacks, it is safe to say that the 34 patients had suffered about 7,500 attacks during their two hundred and forty-two years of disease; despite this the patients insisted that their joints always regained their normal appearance and function, a fact borne out by our own observations.

General Frequency of Attacks.—The character of the individual attacks did not vary much, but the frequency and regularity of attacks varied greatly. The disease had notably changed its pace in 4 cases. In case 1 there had been almost daily attacks for two years and thereafter only four or five a year. In case 20 attacks came only three or four times a year at first and later weekly. One patient (case 32) had about two attacks a year for eight years; then the attacks stopped for six years; thereafter for eleven years he had two to four attacks yearly. In case 33 attacks came twice monthly at first and later almost daily. Thus the pace of the disease quickened notably in some and slowed in others.

In most cases, however, the pace of the disease had been relatively unchanged. To show frequency of attacks at the time of admission,

4. We encountered 4 more typical cases in 1941; biopsy was made in 1 case between the patient's attacks. Articular tissues were grossly and histologically normal.

TABLE 1.—*An Oft Recurring Acute Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residue: Synopsis of Thirty-Four Cases*

Duration

TABLE 1.—*An Oft Recurring Acute Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residue: Synopsis of Thirty-Four Cases*

Case	Date of Admission	Age, Yr.	Sex	Duration of Disease Before Admission, Yr.	Estimated Number of Attacks	Number of Joints Involved in Attack: Usual	Number of Joints Involved in Attack: Maximal	General Frequency of Attacks	Length of Attack: Usual	Length of Attack: Minimal-Maximal	Interval Between Attacks: Usual	Interval Between Attacks: Minimal-Maximal	Sedimentation Rate, Mm. at 1 Hr.	Uric Acid, Mg. per 100 Cc. of Whole Blood	Follow-Up: Condition as of April 1940 *
1	8/ 2/28	21	F	8	"Several hundred"	1	4-5	2 yr.: almost daily 6 yr.:4-5 yearly	12-36 hr.	12 hr.-1 wk.	Few-24 hr.	Few hr.-2 days	..	3.4-4.0	Disease stopped spontaneously September 1928
2	4/11/31	49	M	6	50	1	1	6-10 yearly	6-8 hr.	Hours-1 wk.	2-3 mo.	3 days-sev. mo.	..	4.3	Still having repeated attacks
3	4/20/31	33	F	1	5	1	4	5 in year	4-5 days	1-10 days	.....	1 day-8 mo.	..	3.1	Still repeated attacks but shorter (1-3 days)
4	5/21/31	32	F	8	Hundreds	1	1	Scores yearly	Several days.....		1 mo.	1-3 mo.	..	...	
5	7/22/31	32	M	7	"Hundreds, perhaps thousands"	1	..	Almost daily	2-24 hr.	Hours-2 days	"Few"-24 hr.	Few hr.-few days	..	4.0	Attacks continue as before
6	8/28/31	42	M	10	120	1	3	8-12 yearly	24-36 hr.	.....	Few-24 hr.	Few hr.-2 mo.	..	...	Disease stopped spontaneously (?)
7	2/22/32	32	F	11	300	1	..	About 2 monthly	2-3 days	2-4 days	1 mo.	4-6 wk.	..	3.4	
8	3/28/32	51	M	3	60	1-2	..	2 monthly	8-48 hr.	8 hr.-2 days	2 wk.	3 days-4 mo.	..	4.5	Disease stopped in 1933
9	10/12/32	33	F	2½	250	1	..	2 weekly	12 hr.	12 hr.-2 days	.....	Few hr.-1 mo.	..	...	Disease stopped spontaneously in 1933
10	8/ 6/35	34	M	15	750	1	2	1-2 weekly	36-48 hr.	2-8 days	2-3 days	2-4 days	..	...	
11	11/11/35	39	F	2	300+	1	..	Almost daily	24-36 hr.	1-2 days	2-5 days	1 day-5 mo.	3	3.3	
12	5/18/36	49	F	19	60	1	2	3-4 yearly	Few days	1-10 days	1-2 days	Few hr.-3 days	19	4.9	
13	7/13/36	30	F	1½	60	1	1	1-2 weekly	48 hr.	6-48 hr.	3-4 mo.	1-12 mo.	7	1.6-2.8	
14	7/31/36	45	M	21	750-800	1	1	3 monthly	48 hr.	2-3 days	2-4 days	2-10 days	12	4.0	Attacks continue as before
15	9/19/36	47	M	11/12	50	1	3	4-5 monthly	10-12 hr.	.....	10-14 days	1-45 days	18, 35†	4.0	
16	12/11/36	39	F	6	Hundreds	1	3	Almost daily	8-12 hr.	8-36 hr.	Few days	1 day-2 mo.	10	3.5	Attacks same length but less frequent (4-5 yearly)
17	3/15/37	50	M	14	60	1	..	3-4 yearly	24-48 hr.	1-4 days	Few-24 hr.	Few hr.-4 days	10, 12†	3.1	Attacks same length but a little less frequent (3-4 weekly)
18	3/15/37	44	F	3	180-200	1-3	5	1 yr.: 2-3 weekly 2 yr.: almost daily	24-36 hr.	4-36 hr.	3 mo.	1 wk.-4 mo.	13, 25, 33‡	3.4	Attacks more frequent (weekly) but of same duration; remissions still complete after 17 yr. of disease
19	7/ 9/37	32	M	11/12	130	1	8	3 weekly	6-48 hr.	6-48 hr.	1-2 days	Few hr.-21 days	35†	2.7	Attacks shorter (4-8 hr.) and a little less frequent (4 weekly)
20	1/31/38	73	M	13	600-700	1	2	First: 3-4 yearly Later: weekly	3-24 hr.	3 hr.-3 days ‖	Few-24 hr.	Few hr.-1 day	25†	3.8	
21	2/14/38	51	F	¾	10	1	1	2 in 6 mo. 8 in 3 mo.	8-10 days	1 day-1 mo.	8-10 days	1 day-1 mo.	54†§	4.8	Died 8 mo. later (Sept. 1938) of coronary thrombosis
22	4/ 5/38	36	F	6	200-300	1-2	..	Every few days	2-3 days	1-3 days	1 wk.	6 days-6 mo.	14	3.0	Two attacks since dismissal, each lasting 12 hr.
23	5/16/38	25	F	3	100+	1	4	Every few days	24 hr.	6 hr.-3 days	Few days	.....	51	3.6	Attacks as frequent but a little shorter (6-24 hr.)
24	7/12/38	49	M	10	100-200	1	..	Every few days	3-6 days	6 hr.-6 days	1 wk.	6-10 days	3	...	Attacks shorter (only "overnight") and less frequent (monthly)
25	10/24/38	53	F	6	45	1	3-4	6-8 yearly	1-4 days	Hours-4 days	4-6 wk.	Few days-6 wk.	39	3.0	Attacks continue as before
26	1/13/39	40	F	½	23	2	2	Every few days	2 days	1-2 days	1-2 mo.	2 days-2 mo.	35‡	2.6	Attacks continue as before
27	1/23/39	41	F	2	100	1	3-4	Weekly	3 days	12 hr.-3 days	Few days	Few hr.-2 wk.	35	2.2	Attacks shorter ("just overnight") but as frequent
28	3/29/39	63	F	16	300	1	3	Every 3 wk.	Few days	Few hr.-3 wk.	4-6 days	1-14 days	8‡	2.7	Attacks more frequent (almost daily)
29	6/ 5/39	69	F	¾	32	1-4	..	Weekly	36 hr.	1-4 days	1-4 wk.	1 day-4 wk.	31‡, 35†, 38‡, 38†	3.0	Attacks less frequent but of same length
30	6/22/39	35	M	6	150	1	3	2 monthly	1-2 days	1-2 days	6-10 days	1-3 wk.	30‡	2.7	Attacks about as before
31	7/17/39	33	F	1½	75	1	6	Weekly	2-3 days	1-7 days	1-2 wk.	1 day-2 wk.	25	3.9	Attacks less often (1 monthly) but of same length
32	8/ 8/39	50	M	25	50	1	3	8 yr.; 2 yearly 6 yr.: none 11 yr.: 2-4 yearly	36 hr.	12 hr.-7 days	1-6 days	1-7 days	46‡	2.8	Attacks shorter (4 hr.) and less frequent ("seldom")
33	8/23/39	35	M	1⅔	40	1	1	First: 2 monthly Now: almost daily	12-24 hr.	12 hr.-3 days	3-6 mo.	1 day-8 mo.	9	3.0	Attacks more frequent (monthly) but of same length
34	11/21/39	33	M	10	80-100	1	1	6-8 yearly	1 day	6 hr.-3 days	1-3 wk.	1 day-3 mo.	22†	3.7	Attacks shorter (3-4 hr.) and less frequent (2-3 weekly)
									24-48 hr.	12 hr.-5 days	1-2 mo.	1 day-4 mo.	6, 30†	4.3	3 attacks of usual length since patient's dismissal

* In all cases there were complete remissions after attacks.
† Sedimentation rate during attack.
‡ Sedimentation rate as attack subsided.
§ This patient had serious coronary disease (infarct ?).
‖ In this patient's first attack he was "in a hospital two weeks"; the exact duration of attack is not known but presumably was several days; subsequent attacks were never longer than three days.

the cases are tabulated (table 2): Nine patients were having few attacks, from two to ten, each year; 10, from eighteen to thirty-five; 7, from fifty to sixty, and 8, one hundred to two hundred and fifty or more. Of the last 8 patients, 5 were having attacks almost daily. They would escape an attack on some days; at other times they had a new attack every day, usually in a different site from that of the day before. But even when the same joint was affected on two or more successive days the patients recognized the involvements as separate "attacks," because for at least a few hours each attack cleared up completely, leaving the joint "well" until the next attack. These patients commonly stated that all morning, for example, their joints were entirely normal; then suddenly in the afternoon a joint would become swollen, red, painful and disabled, the involvement lasting a few hours and then disappearing completely in the evening or night. Even if some hours or a day or two later another or the same joint was suddenly involved, their

TABLE 2.—*Approximate Frequency and General Duration of Attacks on Patients' Admission*

Approximate Number of Attacks Each Year	Cases	Duration of Attacks, Days	Cases
250 or more *	5	1 or less	9
150-200	2	1-2	18
100	1	2-3	4
50-60	7	1-4	2
35	3	3-4	1
25	5	4-5	1
18	2	3-6	1
8-10	2	"A few"	2
6-8	2	"Several"	1
2-5	5		

* Almost daily.

conception of these short, isolated bouts as individual attacks seems justified.

Duration of Attacks.—The usual duration of the attacks is given in table 2. In 76 per cent (26) of the cases the attacks usually lasted only from a few hours to three days. Despite their short duration, some of the very short attacks were painful. The minimal length of attacks was three hours in case 20, four hours in case 18 and six hours in cases 13, 19, 22 and 23. The maximal duration of attacks was two days in 10 cases, three days in 7, four days in 5, five days in 1, about one week in 6, ten days in 1 and three weeks in 1 (in this case [case 27], however, many attacks lasted only a few hours). The maximal duration was unstated in 3 cases. Thus in 67 per cent of the cases the longest attacks lasted only from two to five days. Attacks longer than a week were exceptional.

Length of Intervals Between Attacks.—So varied and irregular was the pace of the disease in these cases that the intervals between attacks differed materially in different cases and from time to time in the same case. Most of the patients could not predict when the next attack would occur; in this disease there was no regularity to the attacks as in intermittent hydrarthrosis. The usual interval was as follows: only a few hours (one day or less) in 4 cases, one to two days in 2 cases, two to six days in 5 cases, about one to two weeks in 9 cases, "a few days" in 3 cases, one to two months in 5 cases, two to four months in 3 cases, three to six months in 1 case and unstated in 2 cases. In 5 cases the intervals were on occasion (but not usually) fairly lengthy: six months in cases 21 and 32, eight months in case 2 and a year in case 12. Having had two attacks yearly for eight years, 1 patient (case 32) experienced a spontaneous remission for six years before attacks returned.

Number of Joints Involved in an Attack.—The number of joints affected in an attack was "usually only one" in 29 cases, "one or two" in 2 cases, from one to three in 1 case, two in 1 case and from one to four in 1 case. The maximal number of joints affected in any one attack was one in 7 cases, two in 4 cases, three in 6 cases, three to four in 1 case and four or more in 7 cases; it was unstated in 9 cases. In summary, the great majority of attacks were monarticular; 29 patients usually had only one joint affected; of these 29 patients, at least 7 never had more than one joint involved in any one attack.

Joints Involved.—The disease was ubiquitous; almost any joint in the body was liable to an attack. At one time or another all patients experienced involvement of various finger joints, proximal interphalangeal joints most often, metacarpophalangeal less commonly and terminal phalangeal joints occasionally. The dorsum of the hand was often affected. The knees were affected at one time or another in 32 cases, the feet (various sites) in 25, the wrists in 23, the shoulders in 22, the ankles in 17, the elbows in 16, the jaws in 6, a sternoclavicular joint in 2 and cervical vertebral joints in 1. No patient specifically noted involvement of the lumbar or thoracic portion of the spinal column, but 1 patient said his "spine" had been affected (unfortunately our record does not specify the site). Most of the patients had had from four to six (others had had from eight to eleven) different joints separately affected. But in 1 case (case 28) only two sites, the fingers and knees, had been involved during three hundred attacks.

Joints Most Often Affected.—Patients repeatedly noted that, although any one of many joints had been affected during the years of their dis-

ease, 80 to 90 per cent of their attacks had involved one, two or three favorite sites. Joints most frequently affected were (in order of frequency): those of the fingers (proximal phalangeal or metacarpophalangeal, only occasionally terminal phalangeal), wrists, shoulders, knees, toes and elbows. The metatarsophalangeal joint of a great toe was the favorite site of attacks in 2 cases (cases 1 and 12).

FURTHER CHARACTERISTICS OF THE ARTICULAR ATTACKS

Time of Onset.—In most cases attacks began any time of day or night. Two patients noted their attacks generally on waking at the usual morning hour, but 16 patients stated that most of their attacks came in the late afternoon or evening. Because of the vesperal nature of these attacks we missed seeing several of our outpatients during attacks which had practically disappeared by the next morning. In other cases in which such vesperal attacks occurred, we had to make special arrangements to obtain photographs or biopsies out of hours or to note the effect of such a medicament as epinephrine.

Character of Onset.—The onset of attacks was generally described as sudden; 2 patients said their attacks developed instantaneously. Pain and swelling developed rapidly and were notable within "a matter of minutes" in 2 cases, within a half-hour in another case and within an hour or so in the others.

Rapidity of Progression.—All attacks reached their maximal severity rapidly: in 2 cases within twenty-four hours and much more rapidly in the others. The maximal severity was generally reached in 1 case within half an hour, in 2 cases within one hour, in 4 cases within two hours, in 5 cases within two to four hours and in the rest "within a few hours."

Severity and Character of Pain.—Pain varied considerably from case to case and in a given case from one attack to another. In 4 cases the pain was usually mild or moderate: "a deep steady or throbbing ache"; "a mild throbbing soreness"; an "ache like a bad bruise." In most cases the pain was generally severe: "a severe ache"; "pain like a jumping toothache." One patient said her joints were "bursting with pain and too sore to touch." Several patients characterized the pain as "bursting," "a throbbing, knifelike pain" or a "tight, agonizing pain." One patient felt "as if my joints were grabbed within iron tongs." The pain was called "excruciating" by 3 patients and "vicious" by another. One patient was "almost delirious" with the pain. Two patients (cases 19 and 21) had mild or moderate pain in many attacks but in others required morphine for relief.

In some cases the pain was more severe in the daytime; in 2 cases it was worse "in the evening"; in some cases it was equally severe day and night, but in others it was at its maximum during the night and seriously interfered with sleep.

Redness and Swelling.—In 5 of the cases the periarticular skin generally was not discolored during attacks, but in the other 29 cases articular redness of variable degree was present. It was often moderate but sometimes was pronounced: "dark red"; "fiery red"; "as red as a strawberry."

Articular swelling varied notably, depending on the severity of the attack. The usual swelling was mild in only 4 cases and more severe in the rest. Particularly when finger joints were affected the swellings "flattened out the skin," "ironed the wrinkles out" or made the skin "tense," "shiny" or "waxy."

Degree of Disability with Attacks.—The disability was mild or moderate in some cases and in some attacks, but it was generally considerable and limited the patient's activity. When joints of the upper extremities were affected, several patients could not dress themselves or work efficiently; they did their housework with difficulty, if at all, and "could not type" or play the piano. Some patients had to hold the hand or arm still, put it in a splint or move the affected hand with the other hand. When a foot or knee was affected some patients were only moderately disabled and could walk about in a slipper, perhaps with a limp. Some patients kept off their feet but were not actually confined to bed; 14, however, were so disabled they usually had to go to bed during attacks. One patient (case 18) was "completely disabled and couldn't do a thing," although her attacks were brief (four to thirty-six hours). A physician (case 20) considered several of his attacks sufficiently disabling to require hospitalization.

Constitutional Reactions: Fever; Loss of Appetite or Weight.—There was little if any constitutional reaction during attacks. Despite their frequent severity they were afebrile. Although many of the patients had one or more attacks while under our observation, not one of them had fever therewith, including the one (case 16) who while under our observation had fifteen attacks within twenty-seven days.

Loss of appetite and weight are rather characteristic features of rheumatoid arthritis, but anorexia was not present in any of these cases. Twenty-five (74 per cent) of the 34 patients

had not lost weight (indeed some had gained) despite hundreds of attacks during their one hundred and sixty-eight years of illness.

It would appear, therefore, that significant loss of weight is not a characteristic feature of the disease.

Involvement of Para-Articular Soft Tissues: Para-Arthritis.—Ten (29 per cent) of the patients experienced recurring swellings of para-articular soft tissues. Some patients did not distinguish them clearly from the involvement of articular and periarticular tissues, because the para-articular swellings were often close to joints and often appeared during the articular attacks. Other patients carefully distinguished between the sites of attacks. The attacks of para-arthritis were recurrent but much less frequent than the articular attacks. Usually the para-arthritis appeared as a minor part of an articular attack, but the site of the former was often remote from the site of the latter. Sometimes the para-arthritis appeared without simultaneous arthritis. The attacks of para-arthritis generally came on rather suddenly, sometimes "out of a clear sky" or "within five minutes" and at other times more slowly. The size of swellings varied from the size of a dime (¾ inch [1.9 cm.] in diameter) to considerably larger. Redness was usually present, sometimes faint and at other times "fiery." Pain was sometimes mild but often severe; in cases 2 and 19 it was severe enough to require narcotics for relief. We observed one nocturnal attack involving the soft tissues of the upper part of an arm (case 28) in which the patient walked the floor because of severe pain. Slight pitting was occasionally present, but generally the swellings were rather firm and tender and did not pit appreciably. The attacks of para-arthritis lasted usually from six to twenty-four hours and then disappeared entirely.

Seven of the ten patients with para-arthritis (cases 5, 14, 16, 20, 25, 28 and 34) experienced such attacks while under our observation, sometimes with arthritis and at other times as isolated episodes without arthritis. The lesions we saw varied considerably in diameter (from 1 to 1½ inches or more [2.5 to 3.8 cm.]) and were usually red, tender and slightly elevated above the surrounding tissues. They disappeared within a few hours. The lesions in case 16 have been described in detail (figs. 2*b* and 3*a*). These para-articular lesions were not notably affected by injections of epinephrine.

The lesions were, in our opinion, not truly those of angioneurotic edema or urticaria, although they resembled them somewhat. A dermatologic colleague described the lesions near a heel in case 5 as being "of an urticarial type," "not necessarily an allergic disease." The lesions of urticaria are characterized by the sudden appearance of smooth, slightly elevated patches somewhat whiter than the surrounding skin.[5] Those of angioneurotic edema may be tense and elastic or soft and pitting; the overlying skin may or may not be pink or dusky red.[6] The two conditions are closely related or, according to some, identical. Some physicians consider angioneurotic edema to be a form of giant urticaria which tends to be localized to certain susceptible tissues and recurs in situ. Both urticaria and angioneurotic edema may produce itching, burning and stinging, but their lesions are not particularly tender or painful. Because the para-articular lesions present in our cases were generally tender and painful (sometimes narcotics were required for relief), we regarded them as distinctive lesions.

The sites of these para-articular swellings were, like those of the arthritis, varied, yet curiously consistent in that several patients described swellings identically situated. Usually only one and occasionally two or three sites were involved in each attack of para-arthritis. The sites of these para-articular lesions were as follows (in the order of frequency by case, not by attacks): internal or external malleolus in 4 cases, bottoms of the heels in 3, finger pads or distal phalanges in 3, the flexor surface of a forearm just proximal to the wrist (fig. 2*b*) in 3, thumb pads (fig. 3*a*) in 2 and the dorsal surface of a forearm just proximal to a wrist in 2; in 1 case each, a forearm just distal to the elbow, "anywhere on the palm of the hand," the left thenar eminence, the middle portion of the upper part of an arm, the medial aspect of the right thigh, the lateral aspect of a knee, a knee near the popliteal space, and the achilles tendon.

In case 26 during many of the articular attacks a curious hoarseness without signs of a cold developed. Because of Solis-Cohen's [1] experience in 1 case we wondered whether the attacks of hoarseness might represent swellings of the cricoarytenoid cartilages analogous to those of articular and para-articular tissues.

Intracutaneous or Subcutaneous Nodules.—The nodules in case 16 have been described (figs. 1*a*, 3*a*, 5 and 7). In 2 other cases there were nodules. One patient (case 9) stated that with certain of her articular attacks localized asymmetric nodules developed in thumb pads or on

5. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 19, Philadelphia, W. B. Saunders Company, 1941.

6. Cecil, R. L.: A Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940.

fingers between joints. They were "smaller than a pea" and disappeared with the arthritis. She had none while at the clinic. In another patient (case 34), who frequently noted small, red, tender palmar "sore spots," a small, firm, freely movable subcutaneous nodule developed near a wrist; it disappeared in six or seven days.

Relationship of the Various Lesions.—The three more common reactions, those in articular, periarticular and para-articular tissues, certainly appear to be closely related. The fourth, or rarer, reaction, that producing nodules in intracutaneous or subcutaneous tissues, is also probably a part of the symptom complex. Perhaps it is merely coincidental, but more likely it is a feature of the more severe forms.

SUMMARY OF LABORATORY DATA

Hemoglobin; Erythrocytes; Leukocytes.—Normal values for hemoglobin (for males 14 to 16.7 Gm. and for females 13.5 to 15 Gm. per hundred cubic centimeters of blood) and for erythrocytes (for males 4,500,000 to 5,000,000 and for females 4,000,000 to 4,500,000 per cubic millimeter of blood) were present in 29 (85 per cent) of the 34 cases. Two men had slight reductions in erythrocytes (case 2, 4,450,000; case 32, 4,370,000) but normal values for hemoglobin. One woman (case 12) had a slightly subnormal value for hemoglobin (13.3 Gm.) but a normal number of erythrocytes. Only 2 patients had significant anemia: One, a woman (case 4), had 3,810,000 erythrocytes per cubic millimeter of blood and 12.3 Gm. of hemoglobin per hundred cubic centimeters; the other, a man (case 20), had 4,010,000 erythrocytes and 12.9 Gm. of hemoglobin; he had active coronary disease of which he died eight months later.

Total leukocyte counts made between attacks were normal (5,000 to 8,000 per cubic millimeter of blood) in 21 cases (62 per cent). They were slightly subnormal (3,800 to 4,700) in 3 cases (cases 22, 25, 32) and slightly elevated (9,100 to 16,800) in 10 (cases 10, 14, 15, 17, 18, 20, 24, 30, 33, 34). Total leukocyte counts made between attacks were normal in 12 cases, slightly low in 1 case and slightly elevated (9,500 to 12,400) in 6 cases. Similar counts made during attacks were normal in 4 cases and slightly elevated in 2 (9,600 to 12,400). In other words, the total leukocyte counts were generally normal both during and between attacks but were occasionally slightly or moderately elevated either during or between attacks.

Differential counts made in the intervals between attacks were normal in 9 cases and revealed slight lymphocytosis (36.5 to 48 per cent) in 9 and relative (and total) polymorphonuclear leukocytosis (75 to 88 per cent) in 2. In only 3 cases were the percentages of eosinophils increased, and then but slightly (5.5, 6.5 and 10.5 per cent). Differential counts made during an attack were normal in 3 cases (mild or subsiding attacks) and revealed slight relative lymphocytosis in 2 cases and relative polymorphonuclear leukocytosis (68 to 72 per cent) in 3. Eosinophils were not increased in any case during an attack.

Counts of nonfilamented and filamented leukocytes were made in 12 cases. The percentage of nonfilamented cells was slightly increased (17.5 to 25) in 5, increased to 34.5 in 1 case (case 29) during a remission and normal (16 or less) in the rest.

In summary, total and differential leukocyte counts were often normal both during and between attacks, but there was a tendency toward relative lymphocytosis between attacks and either relative lymphocytosis or polymorphonuclear leukocytosis without eosinophilia during attacks.

One patient (case 16) seen both during and between attacks generally had mild relative lymphocytosis at both times. Another patient (case 19) had moderate lymphocytosis (48 per cent) with 13 per cent of the leukocytes nonfilamented cells between attacks and relative polymorphonuclear leukocytosis (68 per cent) with 23 per cent of the leukocytes nonfilamented cells during an attack, but the total leukocyte counts were normal throughout. In case 28 differential counts were normal between attacks and relative polymorphonuclear leukocytosis (71 to 72 per cent) was present during each of two attacks; the total leukocyte counts were always normal.

Blood Uric Acid.—The concentration of blood uric acid was normal (1.6 to 4.5 mg. per hundred cubic centimeters of whole blood) in 28 of the 30 cases in which it was estimated (table 1). In 2 cases the blood uric acid was slightly elevated: 4.9 mg. in case 11 and 4.8 mg. in case 20, in which heart disease was present. The average value of 32 tests done on 30 patients was 3.4 mg. per hundred cubic centimeters of whole blood. Uric acid partitions (aerobic technic) in 6 cases were normal (table 3).

Miscellaneous Tests on Blood.—The concentrations of various chemical constituents were as follows: Serum calcium was estimated in 13 cases, and the quantity was normal in all. Phosphorus was normal in 5 cases and slightly abnormal in 4 (2.7, 2.8, 4.4 and 2.6 mg. per hundred cubic centimeters of serum). Phosphatase was normal in 3 cases. Cholesterol was normal (160 to 200 mg. per hundred cubic centimeters of plasma) in 2 cases and somewhat elevated

(225 to 315 mg.) in 9. Cholesterol esters were normal (110 to 145 mg. per hundred cubic centimeters of plasma) in 1 case, slightly elevated (167 to 198 mg.) in 7 cases and definitely elevated (277 mg.) in case 27. Lecithin was normal (200 to 250 mg. per hundred cubic centimeters of plasma) in 5 cases, slightly low (187 mg.) in 1 case and slightly high (260 to 266 mg.) in 3 cases. Fatty acids were normal (335 to 350 mg. per hundred cubic centimeters of plasma) in 1 case and slightly low (280 and 312 mg.) in 2 cases, but were increased in 7 (368, 379, 388, 404, 436, 439 and 569 mg.). The total lipids were estimated in 10 cases and were normal (500 to 550 mg. per hundred cubic centimeters of plasma) in none; they were low (455 mg.) in case 16, during a mild attack; elevated (558 to 884 mg.) in 9 cases (case 21, 448 mg.; case 25, 640 mg.; case 27, 884 mg.; case 28, 709 mg.; case 29, 703 mg.; case 30, 598 mg.; case 32, 641 mg.; case 33, 629 mg.; case 34, 564 mg.). In 8 of these 9 cases, the tests were done between attacks. Further studies will be made to determine the significance of this moderate hyperlipemia.

TABLE 3.—*Concentration of Uric Acid in Whole Blood, Plasma and Serum*

Case	Uric Acid, Mg. per 100 Cc.		
	Whole Blood	Plasma	Serum *
16 †.....	3.1	4.4	5.0
19.....	2.8	4.0	5.2
29.....	2.7	2.8	3.0
30.....	3.9	...	5.2
33.....	3.7	5.0	5.3
34.....	4.3	...	5.4

* Normal: less than 6 mg.
† The uric acid was estimated in this case during an attack; in the other cases, between attacks.

Erythrocyte Sedimentation Rates. — Estimations of the sedimentation rate were made in 25 cases (table 1). The rate was normal (less than 20 mm. in one hour, Westergren method) in 10 (40 per cent) of these cases, slightly increased (20 to 40 mm.) in 12 and moderately increased (40 to 54 mm.) in 3. Rates determined between attacks were normal in 8 cases and slightly to moderately elevated in 4. Rates determined during or just after attacks were generally but not always slightly increased. The tendency for rates to be normal between attacks but slightly increased during attacks is illustrated by the figures of cases 14, 17 and 34 (table 1). In case 16 the rate was 10 mm. before an attack and only 12 mm. during an attack. Among those cases in which rates were normal were some in which from one to several attacks a week were occurring and scores to hundreds of attacks had occurred. The average sedimentation rate for the 33 tests done on the 25 patients was only 24 mm. (a much lower average than that in rheumatoid arthritis). Apparently the disease provokes only moderate and transient elevations in the sedimentation rate.

Urinalyses and Wassermann Tests.—These gave normal results in all cases.

Roentgenograms.—Just as these patients did not have symptomatic residues despite their repeated attacks, roentgenographic residues did not develop in joints. Of the 164 roentgenograms of various joints made in the 34 cases, 150 (91 per cent) revealed nothing significant; the remaining 14 (9 per cent) showed changes regarded as unrelated to the chief complaint. The normal roentgenograms were of 44 hands, 20 wrists, 15 elbows, 10 shoulders, 17 feet, 14 ankles, 24 knees, 4 hips and 1 cervical portion and 1 lumbar portion of the spinal column. In many of these regions dozens, even scores, of attacks had occurred; not only were there no abnormalities in articular spaces or contour but there was no general or local decalcification. In some cases we took roentgenograms of as many as eight to twelve joints of a single patient yet found none that revealed anything significant.

Of the 14 roentgenograms that showed significant changes, 3 revealed simply alterations due to bunions; 2 revealed exostotic changes on the dorsa of great toes of 2 elderly patients, a not uncommon finding among elderly persons. The changes in 6 roentgenograms were interpreted as simply due to coincidental osteoarthritis (hypertrophic, senescent) as follows: in the hip and thumb bases of a man 73 years old (case 20) who had never had recurrent acute arthritis in his thumbs; in a hip of an obese woman aged 63; in a knee of a man aged 59, and in the fifth and sixth cervical vertebrae (the usual site for osteoarthritis of the neck) of an elderly woman. One patient who had had 60 recurrent attacks of acute arthritis of the hands, knees and shoulders showed no objective changes in these joints and no roentgenographic changes of his hands; a foot (in which he had *not* had acute recurrent arthritis) showed marked osteoporosis; he had injured this foot two months before and had had it in a cast. A woman aged 69 (case 29) had had acute recurrent arthritis three or four times in each shoulder and twenty or more times in her fingers and wrists; roentgenograms of the hands, the wrists and the right shoulder were normal; that of the left shoulder revealed calcified subdeltoid bursitis. The roentgenograms of a woman (case 12) who had had about sixty short acute attacks involving any one of many joints showed no articular changes in the elbows, hands, wrists, feet, knees or left shoulder, but

there was notable roughening of the right acromion process; her history revealed that she had twice had a painful right shoulder for three months each time, an affair in contrast to her chief complaint of acute short recurring attacks in other joints.

These few evidences of definite articular or osseous change give little support for the idea that the acute recurrent arthritis we are describing produces significant articular damage reflectible in roentgenograms. Since more than 90 per cent of all the roentgenograms of these patients failed to show abnormalities after a total of many decades of illness and hundreds of attacks, it must be concluded that the few articular changes noted were coincidental. When the temporary severity of the clinical symptoms and of the histologic reactions is considered, it is indeed surprising to find no significant roentgenographic residues.

COMMENT ON PATHOLOGIC CHANGES OBSERVED

Our opportunities to study the pathologic changes of palindromic rheumatism have been limited to such gross observations as could be made at the time of biopsies and to histologic study of a few small fragments of tissue. We must acknowledge, therefore, that this experience may not have been sufficient to provide a complete picture of the pathologic processes which occur in this disease. When more material has been examined, some of our impressions regarding these pathologic processes may need revision.

The observations made to date may be summarized as follows:

During an acute attack involving a joint there is rapid onset of acute inflammation with periarticular edema and gross thickening of the capsule of the joint. Polymorphonuclear leukocytes appear within the synovial membrane in large numbers, but eosinophils do not appear in significant numbers. A fibrinopurulent exudate may appear within the cavity of the joint. As the attack subsides the exudate is absorbed from the synovial fluid and the inflammatory cells clear from the synovial membrane. Then a brief period follows during which fibroblasts proliferate actively in the capsule and synovial membrane, but as the attack subsides the signs of inflammation in the capsule and synovia clear rapidly, and eventually the joint structures return to normal.

During intervals between attacks gross and histologic examination of joint tissues reveals no significant evidence of inflammation.

Tendon sheaths may be affected by similar sudden inflammation. During such an attack the walls of these structures show a nonspecific inflammatory process and excess fluid appears in the tendovaginal space. Cultures of this fluid and of the tissues from affected joints have remained sterile. The tendon sheaths, like the joints, are capable of returning to normal after the attack subsides.

The pathologic changes noted in these joints differed from those of rheumatoid arthritis in that no pannus was formed in the cases of palindromic rheumatism and no cartilage was destroyed. Furthermore, the inflammatory reaction within the capsular structures cleared completely once the attack subsided, a phenomenon we should not expect in rheumatoid arthritis. The follicle-like collections of lymphocytes believed by Allison and Ghormley [7] to be characteristic of the reaction in synovial membrane in cases of rheumatoid arthritis were not present in the synovial tissues in the cases of palindromic arthritis.

A subcutaneous nodule presented the histologic reaction of low grade nonspecific inflammation. Necrotic central zones surrounded by palisaded reticuloendothelial cells characterize the subcutaneous nodules of rheumatoid arthritis but were absent from this nodule. Nor did it show the fibrinoid degeneration or collections of cells resembling Aschoff bodies which are characteristic of the subcutaneous nodules of rheumatoid arthritis. The necrotic zones containing crystals of sodium urate which are characteristically present in the subcutaneous tophi of gout were not in evidence.

We cannot draw conclusions as to the possibility of the allergic nature of palindromic rheumatism from our histologic studies. It would be possible to point to certain similarities between the reactions we noted and the reported histologic reactions of urticarial wheals. Apparently a rapid exudation of fluid and inflammatory cells occurs in both conditions. Furthermore, complete and rapid resolution of the pathologic process may take place repeatedly in both conditions. The proliferative features noted in our specimens are not seen in the histologic reactions of wheals, and even were we to accept without question the similarities of these two processes we still should be doubtful as to whether palindromic rheumatism represents an allergic process, because many informed dermatologists today hold that urticaria is often a

7. Allison, N., and Ghormley, R. K.: Diagnosis in Joint Disease: A Clinical and Pathological Study of Arthritis, New York, William Wood & Company, 1931.

manifestation of an infectious rather than an allergic process.

True dermatologic allergy is probably best exemplified in the experimentally produced Arthus phenomenon, as described by Gerlach-Basel,[8] who did not find any specific histologic features and particularly denied the presence of eosinophils in his material.

From these considerations, we can conclude only that palindromic rheumatism is caused by some unknown irritant.

FACTORS PREDISPOSING TO OR PRECIPITATING ATTACKS

Season and Weather.—In general, attacks bore no seasonal relationships. Only 7 of the patients seemed affected by seasons; attacks were more common in winter in 2, in spring in 2, in summer in 2 and in autumn in 1.

Apparently in only 4 cases were attacks more frequent or severe in cold, damp weather; the other patients noted no influence of weather on their disease.

This relative absence of effect of season and weather on this disease is in notable contrast to conditions in rheumatoid arthritis.

Menses.—Three of the 19 female patients believed that their attacks were somewhat worse during menses; the rest saw no definite menstrual influence.

Work; Fatigue; Trauma.—In 2 cases attacks were said to be precipitated occasionally by overwork. The influence of work seemed especially definite in case 16, as described: The patient, a woman, did not entirely escape attacks when resting. She had mild attacks in the hospital when at rest and more severe attacks after deliberately spending long hours at occupational therapy. This state of affairs continued after she returned home, where also work seemed to be a dominant factor in the location and severity of attacks. Nervous or physical fatigue in 2 cases and slight trauma in 4 (for example, gripping the wheel of an automobile for several hours, a slight bruise) seemed to induce attacks, but in most cases neither work nor trauma was considered related to attacks.

Infection.—None of the patients related the attacks to any acute exogenous infection, and only 1 patient considered an infected focus (prostatitis) definitely related to attacks.

Food Sensitivity.—The majority of the patients could offer no explanation for their trouble, but 16 of them made a common suggestion, that sooner or later they had come to suspect the factor of food poisoning or food sensitivity. They had each selected one or more foods as possible offenders; these they had avoided for varying periods. But when, despite this, attacks had continued, most of the patients had given up the idea, particularly because they found they could often eat the supposed offender with impunity. A few patients still held the notion, with varying degrees of conviction, that the attacks were related to food, but no one had been able to prove the point. The foods incriminated belonged to no one food group and need hardly be listed.

AUTHORS' INVESTIGATIONS ON ETIOLOGY

When one of us (P. S. H.) noted his first case of this condition, in 1928, and considered the nature of the attacks, their irregular frequency, sudden onset, short duration and complete remissions despite their relative violence, the idea that they might represent some type of allergic reaction seemed attractive. In recent years several types of "allergic arthritis," generally chronic polyarthritis, sometimes acute monoarthritis or polyarthritis,[9] have been described. But no type of "allergic arthritis" has been definitely established, and the allergic nature of the conditions in the reported cases generally has been regarded as not proved.[10] We share this opinion because no incontrovertible evidence has been offered to indicate that the allegedly allergic acute or chronic arthritis could be consistently prevented or significantly modified by avoidance of the supposed antigen or that attacks could be repeatedly provoked by prescribing the antigen. Notwithstanding such skepticism, we reasoned that if there were such a thing as true allergic arthritis, perhaps this was it. Therefore, certain clinical and thera-

8. Gerlach-Basel: Ueber Beziehungen der Entzündung zum anaphylaktischen Zustand, Verhandl. d. deutsch. path. Gesellsch. **19**:126-131, 1923.

9. (*a*) Boemer, L. C.: Infection, Arthritis and Allergy with an Allergic Dietary Regimen, Illinois M. J. **75**:474-475 (May) 1939. (*b*) Hench, P. S.; Bauer, W.; Dawson, M. H.; Hall, F.; Holbrook, W. P., and Key, J. A.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1937 (Fifth Rheumatism Review), Ann. Int. Med. **12**:1295-1374 (Feb.) 1939. (*c*) Hench, P. S.; Bauer, W.; Dawson, M. H.; Hall, F.; Holbrook, W. P.; Key, J. A., and McEwen, C.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1938 (Sixth Rheumatism Review), ibid. **13**:1655-1739 (March) 1940. (*d*) Wootton, W. T.: An Analysis and Discussion of Positive Food Reactions in Five Hundred Individuals Afflicted with Arthritis or Rheumatoidal Conditions, J. Arkansas M. Soc. **36**:67-69 (Aug.) 1939.

10. Boemer.[9a] Hench and others.[9b] Bauer, W., and Short, C. L.: The Treatment of the Arthritides of Known Origin, New England J. Med. **223**:286-293 (Aug. 22) 1940.

peutic investigations were made in an attempt to prove or disprove the hypothesis.

Does the Disease Represent an Allergic Reaction in Joints?—Familial allergy was not obvious in 24 cases, but 17 close relatives of the remaining 10 patients suffered as follows: 6 from asthma, 3 from hay fever, 3 from known sensitivity to foods (hives), 2 from urticaria of unknown origin, 2 from "eczema" and 1 from migraine. As to the patients themselves, 16 did not have allergic reactions of any sort, 6 had nothing but occasional migraine unrelated to the arthritis and 1 became "dizzy" after taking acetylsalicylic acid. One patient had had attacks of angioneurotic edema two and four years before the onset of his arthritis but none since. Four patients had had occasional attacks due to food sensitivity (abdominal pain, nausea, vomiting and diarrhea beginning within one hour after eating milk, sea food, prunes, oysters or spinach); 1 of these patients also had occasional migraine and another hay fever and asthma. In none of these 4 patients did the articular and gastrointestinal symptoms ever coincide. Six of the patients had had "hives" (urticaria); in 4 of these the hives occurred occasionally and never with arthritis. In 2 cases the attacks of hives generally did not, but occasionally did, coincide with articular attacks; the coincidence was so infrequent that both patients (cases 1 and 15) considered them probably unrelated.

In summary, 16 of the patients had no clinical signs of allergy, and 18 experienced a total of 21 varied possibly allergic reactions. This is not an unusual number to be found among 34 patients of any sort, and the fact that none of the established allergic reactions occurred regularly with the articular reactions seems to speak for the independence of the two conditions.

In 28 cases cutaneous tests were made with various antigens: the common inhalant group; a group of foods to which allergic patients are commonly sensitive, and others including those which the patients themselves suspected might be related to their arthritis. Results were entirely negative in 10 cases and negative except for a few slight reactions in 12 other cases. Such minor reactions were considered of little or no significance, and none of the foods suspected by the patients caused positive cutaneous reactions. Cutaneous reactions of grade 2 developed in only 5 cases; reactions of grade 3 to beef and lamb developed in 1 case. Many of the patients were fed large amounts of the foods to which they were sensitive (even if the reaction was only of grade 1) as well as the foods of which they were suspicious but to which their skin was not sensitive. In no case could we prove to our satisfaction any provocative effect of these foods as far as joints were concerned. Despite the negative reactions to provocative tests, 9 patients accepted a therapeutic test, avoiding the suspected foods for variable periods; only 1 patient believed that the disease was significantly modified thereby.

In a few cases we attempted without success to provoke an attack by histamine, giving a fairly large single (1 mg.) dose intravenously. Results of cold allergy tests made in 5 cases were all negative. One patient (case 2) insisted (and still does) that his attacks were shortened by injections of epinephrine hydrochloride, but such injections in several other cases did not significantly alter the duration or severity of attacks seen by us. As will be noted later, our results with histamine desensitization or with histaminase given orally have not been impressive.

Points favoring an allergic hypothesis were: (1) the suggestive nature of the attacks and their sudden appearance and disappearance without residues; (2) the impressions of several patients that their attacks were caused by certain foods; (3) the occasional presence of clinical allergy of patients and their relatives, and (4) the occasional occurrence of arthritis and hives or angioneurotic edema in the same case. Points against an allergic hypothesis were: (1) the complete absence of orthodox clinical allergy in 47 per cent and the absence of familial allergy in 71 per cent of the cases; (2) the generally negative cutaneous reactions (in 79 per cent of the patients tested); (3) the absence of eosinophilia in blood or affected tissue; (4) the negative results of provocative and therapeutic tests involving suspected foods; (5) the generally negative effect of epinephrine; (6) the negative provocative effect of histamine in large doses and (7) the essentially negative therapeutic effect of histamine desensitization. Dr. L. E. Prickman, who sees much allergic disease at the Mayo Clinic, saw many of these patients with us. In discussing them he recently stated: "The evidence at present points away from an allergic basis for the disease." [11]

Is the Articular Reaction Due to Infection?—The attacks bore no apparent relationship to acute exogenous infection, such as sore throat or influenza. Most of the patients had long since been relieved of infected foci with no or only temporary relief. Only a few infected foci still remained. Tonsils had already been removed in 32 cases (cleanly in 29; with small tags remaining in 3). Moderate infection was

11. Prickman, L. E., in discussion on Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism, Proc. Staff Meet., Mayo Clin. **16**:815 (Dec. 17) 1941.

present in the 2 surviving pairs of tonsils. The entire group had only 4 dead teeth, 3 roots (1 infected) and 3 infected teeth; 15 patients had slight pyorrhea. Among the 19 females were 3 with cervicitis and 3 with cervical erosions. Prostatitis of significant degrees was found in only 4 of the 15 men. Prostatic cultures from 1 patient revealed only Corynebacterium xerosis (diphtheroids). Another patient, a physician with prostatitis grade 4, regarded prostatic massage as a frequent provocative of his attacks. In his case prostatic cultures revealed micrococci and a few streptococci. The same patient had sinusitis, the only instance of this in the entire group.

In a few cases cultures of the nasopharynx were made. In some no significant organisms were recovered. In others hemolytic streptococci were found, but they generally did not produce positive cutaneous reactions in these cases or significant lesions in animals. In 1 case green-producing streptococci from the nasopharynx injected into rabbits produced some periarticular but no other lesions. Green-producing streptococci (from the nasopharynx) in another case (case 20) also produced hemorrhagic muscular and periarticular lesions in rabbits.

Among the several patients who had infected foci removed as therapeutic tests, only 1 (case 23) considered results moderately successful; after tonsillectomy her attacks were milder and less frequent.

Cultures of affected tissues removed at biopsy in 4 cases revealed no bacteria. Agglutination tests for Brucella abortus were negative in 4 cases and slightly positive (1:80) in 1 case; the latter test was considered of no significance.

Does the Disease Represent Angioneurosis?—Dorland's [5] definition of angioneurosis as "any neurosis affecting primarily blood vessels; a disorder of the vasomotor system, as angiospasm, angioparesis, or angioparalysis" illustrates the tenuousness of the entire concept of angioneurosis. Within this generic concept have been included a great variety of syndromes whose only relationship consists in the fact that affected patients display a tendency for blood vessels to react to unknown stimuli by contracting, by dilating or by alternately contracting and dilating. Under this title are grouped such varying conditions as angioneurotic edema, urticaria, intermittent hydrops, scleroderma, erythromelalgia, acroparesthesia, Raynaud's syndrome and many other conditions. Patients affected with angioneurotic disorders are said to be subject to paresthesias, cyanosis or pallor of the fingers and toes, hyperhidrosis, "trophic disorders" of the skin, hair, nails and teeth, increased oculocardiac and vagus reflexes, blushing and pallor of the face.[12] These stigmas of angioneurosis were not significantly present among our patients. Therefore we could not conclude that "angioneurosis" was the cause of the articular and other reactions of palindromic rheumatism.

DIFFERENTIAL DIAGNOSIS

Rheumatoid (Chronic Infectious, Atrophic, Proliferative) Arthritis.—Two varieties of this disease are described, but palindromic rheumatism resembles neither variety. The first, or common, variety (typical, ordinary or primary rheumatoid or atrophic arthritis) generally attacks thin, visceroptotic persons with vasomotor instability. It attacks females two or three times as often as males; it usually affects small joints first and then progresses slowly and rather symmetrically to involve larger, less peripheral joints. Joints are swollen and sore with little if any redness. Little or no fever occurs, and signs of subacute inflammation are usually absent. Partial remissions are frequent, but complete remissions are rare. Sedimentation rates soon increase, sometimes within three weeks of the onset of the disease. Secondary anemia, a slight reduction in blood fats and loss of weight and appetite commonly appear. Roentgenograms soon reveal general decalcification, and within a few months or so more notable changes result from synovial proliferation and destruction of cartilage.

The second, or less common, variety is called "atypical" or "secondary rheumatoid" (or atrophic) arthritis. By those who consider it not a variety but a separate disease, it is called "infective arthritis" or "focal arthritis." [13] Its onset is more acute or subacute than is the usual onset of "primary rheumatoid arthritis"; it appears at times after a definite infection, such as influenza, acute tonsillitis or pharyngitis. A few small or large joints are asymmetrically affected. The disease may progress rapidly, but remissions are supposedly more frequent and more complete than in the first variety. Fever may be present, with considerable articular warmth, redness, swelling and other constitutional signs of infection or toxemia. Roentgenograms at first reveal local articular, rather than general, decalcification but later show articular disintegration similar to that in the first variety.

12. Sachs, B., and Hausman, L.: Nervous and Mental Disorders from Birth Through Adolescence, New York, Paul B. Hoeber, 1926, p. 701.

13. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, T. P.: The Problem of Rheumatism and Arthritis: Review of American and English Literature for 1935 (Third Rheumatism Review), Ann. Int. Med. **10**:754-909 (Dec.) 1936. Hench and others.[9b, c]

Even those who make the greatest distinction between these two conditions agree that the end results are about the same and that no pathologic distinction can be made. Both lead sooner or later to chronic progressive arthritis with articular destruction and deformity. The dominant feature in either variety is the great tendency toward a deforming arthritis with no complete remissions. Even in those cases in which the disease begins with a few preliminary skirmishes and rather complete remissions before becoming progressively chronic, these individual skirmishes last, not hours or days, but weeks or months.

The chief points which distinguish our cases of palindromic rheumatism from instances of rheumatoid arthritis include the following: (1) the totally different pattern of the arthritis (one of numerous short attacks and persistent functional restitution); (2) the tendency for only one or two joints to be involved in an attack; (3) the frequent isolated short attacks of para-arthritis; (4) the general absence of significant constitutional reactions; (5) the relative absence of effect of season and weather; (6) the sedimentation rate, which is relatively normal or only moderately and transiently elevated; (7) the moderate increase (rather than decrease) in blood fats; (8) the persistently negative roentgenograms, and (9) the different pathologic reaction. The greatest and most convincing difference is the persistent absence of chronic arthritis even after scores or hundreds of attacks and years of disease.

It may be argued that, despite these obvious differences between palindromic rheumatism and rheumatoid arthritis, palindromic rheumatism may be merely a newly described variety of rheumatoid arthritis. It may be argued that the differences between the two clinical pictures are no greater than those between, for example, clinically active and progressive tuberculosis in 1 case and a small healed ghon complex in another. It might be suggested that perhaps the distinctions between palindromic rheumatism and rheumatoid arthritis result, not from any dissimilarity in the causal agents of the two conditions, but from different tissue reactions or immune responses of the host. This argument will gain force only if prolonged study of our cases and of similar cases indicates that chronic articular residues with pathologic reactions indistinguishable from those of classic rheumatoid arthritis do eventually develop in a notable number of cases of our palindromic rheumatism. On the basis of our experience[14] to date we do not consider palindromic rheumatism merely a newly described "palindromic variety" of rheumatoid arthritis.

Periarticular Fibrositis.—The four commonest articular diseases which attack joints repeatedly and then disappear completely are periarticular fibrositis, intermittent hydrarthrosis, rheumatic fever and gout. Obviously our cases did not represent ordinary primary fibrositis. In this condition there are practically no redness or swelling of joints, no recurrent para-articular swelling and no seropurulent exudate.

Intermittent Hydrarthrosis.—This disease rarely affects any joint but knees, is rarely painful and attacks joints at regularly spaced intervals. Its pattern and progression are different from those which we have described for palindromic rheumatism. In our cases of palindromic rheumatism a transient intra-articular exudate was sometimes present but was overshadowed by the more noticeable periarticular inflammation, and the attacks were irregularly, not regularly, spaced.

Rheumatic Fever.—This is characterized by recurrent attacks of acute febrile polyarthritis of some weeks' duration with residual carditis. In our cases attacks were afebrile, short and usually monarticular, and carditis was absent in all cases, even those of many years' duration.

Gout.—Our cases presented certain features suggestive of acute gouty arthritis: the sudden onset of the attacks, appearing sometimes during the night, the rapid progression to maximal disability, the occasional involvement of great toes, the pain, which was often severe and sometimes worse at night, and the rapidity and completeness of the remissions. But none of our patients had hyperuricemia, tophi on the ears, urates in the joint tissues or the roentgenographic changes of gout even after years of disease. Nor were any of our patients relieved by a regimen for gout or made worse by high purine, high fat diets. In our cases the attacks were generally much shorter and much more frequent than even those of severe, progressive gout. Had gout been present, its characteristic features surely would have developed in some cases after so many attacks.

Angioneural Arthrosis (Solis-Cohen).—While continuing our search for a report of a condition resembling ours, in 1935 we came on a relatively old clinical description of cases somewhat resembling ours, a report by Solis-Cohen of a condition which he called angioneural arthrosis

14. Hench, P. S., in discussion on Hench, P. S.: An Oft Recurring Disease of Joints (Arthritis, Peri-arthritis, Para-Arthritis) Apparently Producing No Articular Residues, J. A. M. A. **115**:2208 (Dec. 21) 1940.

(periarthrosis, "pararthrosis") and which he believed to be commonly mistaken for gout or rheumatism. He reported 6 cases in 1911 and 21 more in 1913. His reports unfortunately escaped the attention not only of internists but of rheumatologists as well. In these cases painful swelling in and around joints appeared at regular or irregular intervals. Affected were joints alone in 11 per cent; soft tissues alone in 30 per cent and both joints and nearby soft tissues in 59 per cent of the 27 cases. The individual attacks lasted from a few hours to many weeks and then disappeared completely. Attacks were polyarticular in 70 per cent and monarticular in 30 per cent of cases. Almost any joint was liable to involvement, but especially the more peripheral joints: fingers, wrists, elbows, toes or a big toe, ankles and knees. No joint was immune; vertebral and temporomaxillary joints were sometimes involved. In one case laryngoscopic examination revealed involvement of the cricoarytenoid cartilages. The intervals between attacks were regular in some cases and irregular in others and lasted from a few days or weeks to months or years. Thus attacks came daily or weekly in some cases and only four or five times a year in others. Spontaneous remissions for months or years occasionally occurred. Solis-Cohen's 27 patients had had a total of 110 (average 4) attacks (a much smaller average than in our cases). The sex incidence was 45 per cent males and 55 per cent females. Thirty per cent of his patients were less than 12 years of age; 45 per cent, from 12 to 25; 18 per cent, from 25 to 50, and 7 per cent, from 50 to 70. It is not stated whether this refers to the ages of the patients when first affected or when first seen by Solis-Cohen.

The swellings were ascribed either to intra-articular effusions or to nonpitting edema of periarticular tissues or to both. They were generally but not always painful, pain being moderate to agonizing. They were generally associated with red or cyanotic discoloration of the skin, occasionally with eruptions (vesicles, bullae) and also with a subjective (but not an objective) sensation of local heat. Fever was never present in 60 per cent of the cases but was present in some attacks in 22 per cent and in all attacks in 18 per cent. When present the fever was "continuous, recurrent or intermittent." It was irregular and "utterly capricious" in some cases and paroxysmal and "apparently periodic" in others. Fever lasted for a few (twelve to seventy-two) hours or a few days. It was inferred that eosinophilia or leukopenia was sometimes present. Many of the patients presented "the typical dermographic, ocular and nail-bed signs" of vasomotor or autonomic ataxia. Excitants of the attacks were fatigue, emotion, toxemia and atmospheric changes.

Solis-Cohen regarded this condition as one species of autonomic ataxia, a "slighter form" of articular reaction than intermittent hydrarthrosis. To him the articular attacks represented recurrent angioneurotic crises in cases in which the characteristic stigmas of angioneural imbalance were present. He made no articular biopsies but interpreted the effusions as due to angioneurotic edema; in angioneural arthroses "we are not dealing with a true inflammation-arthritis." Treatment was based on this concept and included: for the acute stage local and sometimes general rest, a liquid or soft diet and "elimination"; for the convalescent stage "roborants and hematinics"; between attacks measures to "re-educate vascular reactions" and to "restore vasomotor tone."

TABLE 4.—*Points of Difference Between Authors' Cases and Those of Solis-Cohen and of Kahlmeter*

	Cases of Solis-Cohen ("Angioneural Arthrosis")	Cases of Kahlmeter ("Allergic Rheumatism?")	Our Cases (Palindromic Rheumatism)
Patients less than 12 years of age	30%	.....	None
Polyarticular attacks	70%	Few	Few
Fever	40%	Occasional	None
Cutaneous eruptions	Occasionally erythema; vesicles; bullae	Occasionally erysipeloid rash	None
Duration of attacks	Sometimes "many weeks"	Rarely more than 1 week	Rarely 1 week
Intervals	Sometimes regular	Irregular	Irregular
Allergic reactions	Common	Common	Rare
Pathologic reaction in joints	"Transudate" (assumption)	Serous exudate (assumption)	Inflammatory exudate

Our cases resemble these in many respects, but certain noteworthy differences are apparent (table 4): 1. In Solis-Cohen's cases "the chief symptomatic elements were pain, swelling, discoloration and fever." Forty per cent of his patients had fever in some or all of their attacks. None of our patients had fever during their attacks. 2. In Solis-Cohen's cases the attacks sometimes lasted "many weeks"; in our cases, only a few hours or days, rarely more than a week. 3. In Solis-Cohen's cases attacks were polyarticular in 70 per cent and monarticular in 30 per cent. In our cases the majority of attacks were monarticular. 4. Solis-Cohen emphasized the frequent occurrence of hives, dermographism and other evidences of vasomotor ataxia in his cases and also the occasional presence of vesicular or bullous cutaneous lesions. Our patients

exhibited no vesicles or bullae; 20 per cent had had hives or angioneurotic edema at some time or other, but rarely accompanying their attacks of arthritis. 5. In 30 per cent of Solis-Cohen's cases the disease developed before the age of 12 years; this was true in none of our cases. 6. Solis-Cohen considered the exudation to be a transudate or an edema and the articular reaction to be, not true inflammation, not arthritis, but "arthrosis." He presented no pathologic data on his cases and hence could not prove his concept. Our data reveal the presence of a true inflammatory exudate; therefore the term "arthrosis" is inappropriate, at least for our cases.

Despite these important differences the resemblances between the two conditions are too great to be dismissed lightly. Solis-Cohen presented no photographs or roentgenograms of his cases and no data on pathologic changes or on blood urates (the latter were hardly available in 1913). Perhaps he noted some cases similar to ours but adulterated his description of them by including some extraneous cases. If this is not so, we cannot, on the basis of our experience to date, identify the condition in our cases with his disease which was so often febrile and polyarticular.[15]

"Allergic Rheumatism" (Kahlmeter). — Although, with others, Kahlmeter[2] generally regarded the so-called allergic types of arthritis skeptically, in 1939 he noted one form which he considered might be truly allergic. Under the term *rhumatisme articulaire et périarticulaire d'une nature réellement allergique* he described 54 cases observed within five years. Twenty-two per cent of the patients were males and 78 per cent females. Most of them were less than 50 years of age; 40 per cent were from 31 to 40 years. Attacks of "local edema" involving articular or periarticular tissues, tendons or subcutaneous connective tissue distant from joints recurred at irregular intervals. No articular biopsies were made. The edema was assumed to be a serous, not an inflammatory, exudate, and there was neither local heat nor redness. The location of the edema was capricious, but usually only one or two joints or adjacent sites were affected at a given time. Articular swellings were often afebrile, sometimes associated with a mild fleeting fever and an erysipeloid or erysipelatous skin rash. The attacks lasted generally from several (twenty-four to forty-eight) hours to several days, occasionally seven to fourteen days, and then invariably disappeared completely, leaving no subjective or objective residues—"certainly no progressive joint lesion." The intervals between attacks were from one or two days to several months.

Allergic reactions were common among the relatives as well as among the patients themselves, in most of whom the articular attacks alternated or coincided with certain allergic reactions. Of these patients, 35 per cent had had urticaria, 13 per cent asthma, 11 per cent Quincke's edema and 9 per cent migraine. Some patients noted nausea, diarrhea or lassitude for a day before attacks. Eight cases in which the condition had been present for from one to twenty years were described briefly. A mildly febrile urticaria which after a few days was associated with edematous swelling of one or two finger joints or tendon sheaths developed frequently in 1 case; "several days" later the urticaria, fever and arthritis disappeared together. In Kahlmeter's cases there was no anemia; total leukocyte counts were normal or somewhat low (about 5,000): there was a "constant" relative lymphocytosis (38 to 52 per cent) without eosinophilia (1 to 2 per cent). Sedimentation rates were normal or only mildly and fleetingly elevated during attacks (the highest value mentioned was 33 mm.). No data on pathologic changes or roentgenograms were given. With reservations Kahlmeter regarded the condition as allergic because of the frequent allergic reactions of patients and their relatives and because tuberculin, Dick and Schick tests revealed notable hypersensitivity of the skin — "nonspecific allergic reactions." Despite this Kahlmeter was sufficiently uncertain of the cause of the disease to express the title of his paper in the form of a query "Are There Forms of Articular and Periarticular Rheumatism of a Nature Truly Allergic?" The matter of sensitivity to food was not considered. One patient was given injections of tuberculin in "homeopathic doses" (0.5 cu. mm.) during twelve weeks. An attack developed regularly two days after each injection, but the duration of attacks was gradually shortened from several days to two hours and then the attacks disappeared. Three patients were given ten injections of sodium keratinate, which were assumed successful in stopping the disease.

These cases resemble ours even more than those of Solis-Cohen (table 4), but again certain differences must be noted. Local redness was

15. On Jan. 8, 1942, Dr. Solis-Cohen wrote the authors: "At first sight the two groups of cases [that described by Solis-Cohen and that described herein] seem to differ in so many important particulars that they may be provisionally classified as, at least, different varieties."

usually absent in Kahlmeter's cases; it was usually present in ours. Kahlmeter's patients occasionally had fever and erysipeloid rashes; none of ours did. The frequency of the common allergic reactions was much greater in his cases than in ours.

The similarities between Solis-Cohen's, Kahlmeter's and our groups of cases are more striking than their differences. Perhaps they represent the same disease. Perhaps further experience will bring us cases with the missing features (fever, rashes, impressively coincidental acute allergy, and so forth), or perhaps pruning and more rigorous selection of cases by Solis-Cohen and Kahlmeter will remove the differences, but for the present the differences should be noted.

PROPOSED TERMINOLOGY

Were we prepared to assume (which we cannot yet do) that our cases were instances of the same condition as the "angioneural arthrosis" of Solis-Cohen or the "allergic rheumatism" of Kahlmeter, we still could not approve the adoption of either of these two terms for the disease we are describing, because the presence of an angioneurosis or of an allergic reaction as the basic cause remains unproved. We have avoided the use of a term which would commit us to an unproved etiologic concept. Furthermore, the term "arthrosis" is not suitable for a condition a feature of which is a true inflammatory exudate. Vague though it is, the term "rheumatism" (used in the broad American, and not in the specific English, sense) seems more suitable than "arthritis," because the former term is more comprehensive and hence more applicable to a condition which produces not just arthritis but also periarthritis, para-arthritis and occasionally subcutaneous nodules. Such simple terms as "recurrent rheumatism," "intermittent rheumatism" or "remitting rheumatism" are unsatisfactory for our disease because they are either too nonspecific and indefinite or too suggestive of recurrent rheumatic fever or intermittent hydrarthrosis. The nicknames "hit and run rheumatism" and "phantom rheumatism" proved useful for a time to satisfy the curiosity of patients and their natural desire for at least a name for their disease, but such nicknames are of course unsuitable as permanent designations.

When an etiologic term cannot be applied, a distinctive descriptive term should be used. Such a designation we found in the term "palindromic rheumatism," suggested to us by Profs. A. D. Fraser and Atcheson L. Hench, of the departments of ancient languages and English literature, respectively, of the University of Virginia. "Palindromic" means simply "recurring" or "returning" and is so defined in current nonmedical and medical dictionaries. It is derived from the Greek word παλινδρομέω which means literally "to run back." The verb and its related adjective and noun were used by Hippocrates [16] or by his contemporaries. Used in a strictly nonspecific sense, they are found, not in the Hippocratic canon, the proved writings of Hippocrates, but in the Hippocratic corpus, the body of writings ascribed to Hippocrates, some of which may have been written by his contemporaries. In "De morbis vulgaribus" the Hippocratic writer used the adjective "palindromic" referring to recurring erysipelas or to recurring, retreating or subsiding abscesses. Prof. James Constantine, of the University of Virginia, helped us to trace and define later uses of the term. The medieval Byzantine scholar Hesychius used the word as meaning to recur or retreat; when applied to disease it designated one which either returned or disappeared. The new Liddell and Scott Greek lexicon [17] defines palindromic, used in a medical sense, as meaning "recurring" or "subsiding without coming to a head."

Since the most obvious and characteristic features of the condition we have described are its frequent recurrences, its attacks and retreats, the term "palindromic" seems indeed fitting as it is descriptive, yet sufficiently unused in recent writings to be distinctive to modern ears. Hence we propose to use in a specific sense, that is, for this specific condition, this term heretofore used by Hippocrates and other writers in a nonspecific sense. As one of our advisers aptly said, "What was good enough for Hippocrates ought to be good enough for you." The designation "palindromic rheumatism" has been approved for inclusion in the "Standard Nomenclature of Disease" and appears, with numerical designation, in the third edition. We believe it will be useful and satisfactory until a better (etiologic) term can be applied.

TREATMENT

Numerous treatments had been used by our patients before their coming to the clinic, generally without success; they included removal of infected foci and use of vaccines, bee venom and various medicines. Most of the patients had fallen back on the use of heat and analgesics during attacks.

16. Hippocrates: De morbis vulgaribus, liber secundus, in Opera omnia, translated and edited by A. Foësius, Geneva, S. Chouët, 1657, p. 1035; Oeconomia Hippocratis alphabeti serie distincta, ibid., 1662, p. 289.

17. Liddell, H. G., and Scott, R.: A Greek-English Lexicon, revised and augmented by H. S. Jones, Oxford, Clarendon Press, 1940, vol. 2, p. 1292.

Our first remedies were predicated on the idea that the disease might be allergic; later, measures to combat some possible infection were instituted. Neither plan of attack has produced notable results, as the follow-up data in table 1 indicate. Our results with epinephrine, ephedrine, amphetamine, ergotamine tartrate, diets low in purine, diets free of supposed food antigens, removal of infected foci and autogenous vaccines have all been relatively unsuccessful. Histaminase was used without results in 3 cases. Histamine desensitization has given definitely negative results for 3 patients and equivocal results for 4 others, who, however, insisted that their attacks had become less severe or less frequent since histamine was used. Further observations are necessary before making a final evaluation. Some patients have continued to rely on diathermy, hot packs or other forms of heat. Injections of triple typhoid vaccine may have been responsible for the temporary relief noted in case 16.

A few remedies used by certain patients since their dismissal from the clinic are worthy of comment. Sulfanilamide did not affect the disease in 2 cases (cases 20 and 34). One patient (case 17) felt "75 per cent better for a year" after having fever therapy, but he still has his attacks. One patient (case 13) thought she was partially relieved by taking "dicalcium wafers," and another patient (case 8), a physician, ascribed the temporary disappearance of his disease to the daily use of 75 to 100 grains (4.8 to 6.5 Gm.) of calcium gluconate; later the disease recurred only to disappear completely again after total alveolectomy. One patient (case 5), who ascribed his attacks to nervous fatigue, wrote that his attacks are less severe since he "quit the oil business, became a druggist and began to take phenobarbital daily." Another patient successfully employed an even more novel remedy. She adopted a baby, quit worrying about herself and lost her attacks. Her statement is food for thought.

PROGNOSIS: END RESULTS

Our follow-up study has revealed the following facts: In 4 cases the patients obtained an apparent "cure" within a few months after leaving the clinic and have had no further attacks for from seven to eleven years. Cessation of the attacks occurred spontaneously in 3 of these cases and presumably as a result of treatment with calcium gluconate or of alveolectomy in the other. In 5 cases attacks have become shorter and less frequent; in 1 of these the patient, a local resident, is apparently obtaining a spontaneous cure. His attacks are becoming much milder and much less frequent. In 3 cases attacks are shorter but as frequent as always. In 4 cases attacks are less frequent but their duration remains the same. The condition of 7 patients remains unchanged as to frequency, severity and duration of attacks. Three patients are perhaps worse in that their attacks are more frequent although not longer. One patient died of coronary disease. Seven patients have not answered our inquiries.

Thus of the 27 patients of whose condition we know, 15 per cent are now well, 44 per cent (12) are improved somewhat though not notably, 26 per cent (7) are as before, 11 per cent (3) are somewhat worse and 1 (4 per cent) died of causes unrelated to the arthritis. Hence the prognosis for a spontaneous cure or one induced by the remedies noted herein is only fair. Obviously the disease can be persistent, but if these experiences are characteristic, patients are more likely to become somewhat better than somewhat worse. There appears to be little or no tendency for attacks to lengthen and become confluent, that is, chronic, in a given joint. The disease is a great nuisance to many, a notable handicap to some. But despite the thousands of attacks suffered during a grand total of at least three hundred and seven years of illness (two hundred and forty-two years prior to plus sixty-five years since admission), not a single joint has been crippled permanently.

The Mayo Clinic.

COMPARATIVE STUDY OF ANALGESIC EFFECT OF MORPHINE SULFATE AND MONOACETYLMORPHINE

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A comparative study has been made of the analgesic effects on human beings of morphine sulfate and one of its derivatives, monoacetylmorphine.[1] Twenty-four normal males, ranging in age from 17 to 25 years, were used as test subjects in the experiments. Pain was produced by means of heat stimulation of the skin of the forehead by means of a modified Hardy-Wolff [2] cutaneous heat radiation apparatus. Two components of the pain experience were studied: first, the threshold of perception of pain, and, second, the threshold of reaction to pain. The accuracy of the method had been established previously by control observations on the variations in sensitivity to pain in 200 normal subjects.[3] The measure of the threshold of pain perception was taken to be the lowest strength of stimulus necessary to cause a sharp prick or piercing jab following a sensation of diffuse, burning heat. The threshold of pain reaction was taken to be the lowest measurable stimulus needed to cause wincing (observed as a beginning contraction of the muscles of the outer canthus of the eye).

In the original control study it had been found that for subjects on whom repeated observations were made the error inherent in the estimation of pain perception was not more than ± 3 per cent, while the error for pain reaction showed individual variations of from ± 5 to ± 8 per cent. The purpose of the present study was to determine the relative effectiveness of morphine sulfate and monoacetylmorphine in modifying the perception of pain and the reaction to it. A further study of the analgesic effects of monoacetylmorphine was made with a group of 13 normal subjects, a compression method resulting in muscular ischemia being used for the production of pain. Throughout all the studies careful observations were made on the side reactions associated with the administration of the two drugs.

METHOD

A. Cutaneous Pain Caused by Heat Radiation.—The source of the pain stimulus was a 1,000 watt Mazda lamp. The light from the lamp was focused by two 4 inch (10.2 cm.) plano convex lenses through a 2.5 by 2.5 cm. aperture onto a blackened area in the midforehead. Each exposure to the heat stimulus was maintained for exactly three seconds by a shutter operated by a telechron motor. The intensity of the stimulus was varied uniformly by a wire rheostat. The amount of heat used was measured directly by a radiometer and a potentiometer, and the results were expressed in absolute end point values of gram calories per second per square centimeter of skin surface. Each subject was tested under standard conditions and on two different occasions, in order to familiarize him with the test and to establish his normal thresholds for perception of and reaction to pain. A description of the end point for perception of pain was elicited by a neutral question technic, so that any error of interpretation due to suggestion might be avoided. After the subjective end point for pain was established, the objective measure of the end point of reaction to pain was taken. Both end points of sensitivity to pain were again determined for each subject immediately before the administration of the drug to be tested. Observations on the drug's effect were made at half-hour intervals for the next four hours; at the same time, questions were asked and notations made as to any resultant side reactions.

Each drug was administered subcutaneously, and its dose was standardized as follows: morphine sulfate, 0.24 mg., and monoacetylmorphine hydrochloride, 0.06 mg. per kilogram of body weight. With this ratio, one-

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital.

1. Dr. Nathan B. Eddy, of the National Institute of Health, Bethesda, Md., furnished an adequate supply of this drug for experimental purposes.

2. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Investigation **19**:649-657, 1940.

3. Chapman, W. P., and Jones, C. M.: Variations in Cutaneous and Visceral Pain Sensitivity in Normal Subjects, J. Clin. Investigation **23**:81-91, 1944.

fourth as much monoacetylmorphine as morphine sulfate [4] was used.

Preparations of the drugs for subcutaneous use were made as follows: Morphine sulfate was prepared as an aqueous solution containing 16.8 mg. per cubic centimeter of distilled water, and monoacetylmorphine hydrochloride, as an aqueous solution containing 4.2 mg. per cubic centimeter of distilled water.

Originally each solution was sterilized by being passed through a Seitz filter. The filtered solutions were then placed in boron glass containers (army vaccine type) and kept at room temperature. At the end of sixty days it was found that the analgesic value of the solution of monoacetylmorphine had diminished to a point at which no definite effect could be demonstrated, whereas no apparent change had occurred in the solution of morphine sulfate. Because of this apparent deterioration, the results of all experiments up to this point were discarded. Subsequently, the solution of each drug was sterilized by boiling, at first for fifteen minutes and later for five minutes. In this communication the only results reported are those which followed the use of the freshly prepared solutions, from which apparently full therapeutic results were obtained.

Although no definite explanation can be given for the apparent deterioration of the solutions of monoacetylmorphine, some observations may provide a clue. Determinations of p_H were made with the electropotentiometer on the filtered aqueous solutions which had been kept for sixty days at room temperature, as well as on the freshly prepared solutions. For the former solutions readings of p_H as low as 2.5 were obtained, while for the latter the values for the p_H were in the vicinity of 5. Further studies are in progress to determine the stability of such solutions under varying conditions.

B. Pain Due to Muscular Ischemia.—Severe aching pain of the forearm and hand was produced by voluntary, uniform, periodic contraction of the hand under conditions of complete vascular occlusion. The subject was examined in the horizontal position with a sphygmomanometer cuff on each arm, and readings of the blood pressure were recorded at intervals. The cuff on the left arm was inflated and maintained at a pressure of 200 mm. of mercury throughout the experiment, the circulation in the portion of the arm distal to the cuff being thus completely occluded. Basal blood pressure readings were taken on the right arm over a preliminary five minute period. The subject was then asked to contract his left hand and forearm at intervals of one second for given periods during a total elapsed time of six hundred seconds. Readings of the blood pressure (right arm) were taken at the end of thirty and sixty seconds, and thereafter at one minute intervals during the ten minute test period and for five additional minutes after the pressure on the left arm was released. Since voluntary muscular contractions could not be continued for more than ninety to one hundred and twenty seconds because of fatigue and pain, tests for the effects of contraction were repeated at the end of two hundred seconds and, again, at the end of four hundred seconds of elapsed time. The number of muscular contractions for each period was charted. During the tests, the examiner made periodic attempts to estimate the severity of pain experienced in the left arm by asking "Is the pain which is now beginning more severe or less severe than, or the same as, that just experienced?"

It is obvious that this method of production of pain, a modification of the procedure standardized by Alam and Smirk,[5] is less accurate than that used in the production of cutaneous pain by measured amounts of heat, but it was thought that the results were of interest for purposes of comparison.

After control observations had been completed, the entire test was repeated after the subcutaneous administration of monoacetylmorphine, in the same dose as in the preceding experiments. The results of the tests, that is, the number of contractions performed and the pain experienced by individual subjects, with the drug were compared with the results without the drugs.

RESULTS

A. Cutaneous Pain Caused by Heat Radiation.—Morphine Sulfate: The effects of this drug on the threshold of perception of cutaneous pain over a four hour period are shown graphically in table 1. At the end of one-half hour the average elevation of threshold over the basal, or initial, level was approximately 10 per cent. For all the patients the individual range varied from zero to 35 per cent. At the end of one hour the average elevation was 17 per cent, with a range of from zero to 49 per cent in individual subjects. The greatest elevation of threshold was obtained at the end of one and one-half hours, with an average of 20 per cent and an individual variation of from zero to 56 per cent. Thereafter, the analgesic effect diminished, with an average decrease at the end of two hours to a level 16 per cent above the control figure. At the end of two and one-half hours the average elevation above the initial threshold was 11 per cent; at the end of three hours, 17 per cent; at the end of three and a half hours, 11 per cent, and at the final observation, made four hours after the administration of the drug, 10 per cent.

Although the measurable effects of the drug varied considerably in individual subjects, only 2 failed to show any increase in threshold of pain perception throughout the course of the experiment. (A complete record of the individual values following the use of the drugs is found in table 1.)

As a general rule, the increases in the threshold of reaction to pain paralleled those in the threshold of perception of pain. In about one-fourth the experiments, definite measurements

4. Such a ratio was originally suggested by Dr. Nathan B. Eddy. According to information received from Dr. Lyndon F. Small, of the United States Public Health Service, Bethesda, Md., the actual substances used for comparison were morphine sulfate pentahydrate, containing 75.2 per cent of the alkaloid, and monoacetylmorphine hydrochloride, a hydrated salt containing 78.9 per cent of the alkaloid.

5. Alam, M., and Smirk, F. H.: Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure, Clin. Sc. **3**:253-258, 1938.

of the effect of the drug on reaction to pain could not be obtained, because the initial elevation in the threshold of perception of pain would have necessitated the use of a stimulus capable of blistering the skin at, or before, the point of actual reaction to pain was reached. Such a result, obviously, would have invalidated the thresholds both of perception and of reaction to pain in subsequent studies. In the 30 to 40 per cent of subjects whose increase in threshold of reaction to pain did not parallel their increase in threshold of perception of pain, the spread between the two end points ranged from 5 to 49 per cent. In some of these subjects the drug apparently had a relatively greater effect in raising the threshold of reaction to pain than in raising the threshold of perception of pain.

Monoacetylmorphine: The effects of this drug are also charted in table 1. At the end of one-half hour there was an average increase in the threshold of pain perception of 17 per cent, although, again, the individual variations ranged from zero to 56 per cent. At the end of one hour the average elevation of threshold was 19 per cent, once more with a wide range, from zero to 56 per cent. As with morphine sulfate, the greatest elevation of the threshold of perception of pain was obtained at the end of one and one-half hours, at which time the average increase for the entire group was 19 per cent, with a range of from zero to 42 per cent above the initial control figures. From this point there was a gradual decrease until, at the end of four hours, the average elevation of threshold was

TABLE 1.—*Individual Increases* (Percentile) in Threshold of Pain Perception Following Administration of Morphine Sulfate and Monoacetylmorphine to Twenty-Four Normal Subjects*

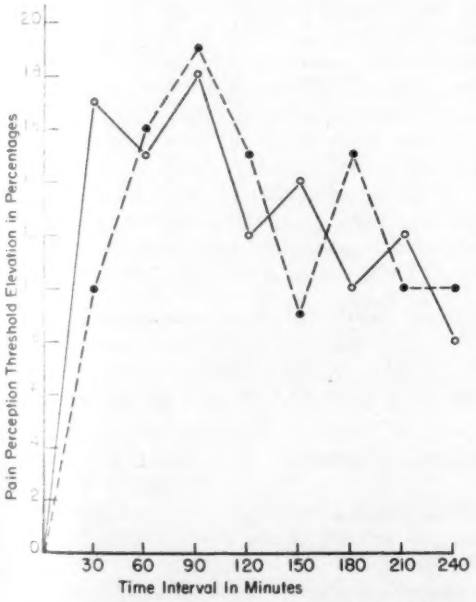
Time		30 Min.		60 Min.		90 Min.		120 Min.		150 Min.		180 Min.		210 Min.		240 Min.	
Drug †.....		MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM
Subject	Test																
1	A	0	7	0	14	0	..	0	21	0	7	0	21	0	7	0	0
	B	0	0	0	11	0	7	0	11	0	18	0	7	0	7	0	14
2	A	14	0	0	42	14	21	14	0	21	..	..	0	28	..	28	0
	B	..	0	42	0	56	28	28	0	..	..	28	..	..	..	..	..
3	A	0	14	0	0	0	0	0	0	0	0	..	..	..	..	..	..
4	A	21	..	21	14	21	35	21	18	21	14	21	11	21	18	0	0
5	A	7	42	35	..	21	18	21	11	21	..	11	11	0	11	0	7
	B	..	25	..	11	..	11	..	11	..	11	..	..	..	4	..	4
6	A	..	21	14	21	0	..	0	14	7	..	..	..	0	..	0	..
	B	..	..	..	18	..	..	..	..	..	..	..	..	..	..	..	..
7	A	0	14	14	14	14	14	14	14	..	0	7	0	0	0	0	0
	B	..	25	..	18	..	18	..	14	..	..	..	11	..	0	..	0
8	A	..	25	46	18	..	18	60	7	..	..	60	..	18	11	..	4
9	A	0	35	11	21	49	7	..	0	0	0	35	0	..	0	..	0
10	A	..	0	42	28	35	14	11	14	14	14	..	14	14	14	..	7
	B	..	..	..	25	..	32	..	11	..	..	..	..	..	4	..	0
11	A	35	28	0	28	0	18	..	..	..	..	..	..	..	..	..	..
12	A	7	32	7	35	7	28	4	..	..	..	..	..	..	..	..	..
	B	..	..	..	28	..	..	..	..	..	..	..	..	..	..	..	..
13	A	0	14	14	7	0	0	0	0	14	..	14	..	0	..	..	..
14	A	21	0	21	7	21	0	21	0	..	..	0	14	..	35	0	28
	B	0	0	0	14	0	21	0	14	..	..	0	14	0	14	0	..
15	A	35	7	49	7	49	0	49	0	49	..	49	0	35	9	..	7
	B	14	0	14	42	14	42	0	..	0	..	7	35	..	14	7	11
16	A	21	18	21	7	..	7	21	..	11	0	11	0	11	0	11	0
	B	0	0	14	21	21	0	14	0	..	..	0	0	..	..	..	..
17	A	0	..	0	14	42	..	14	14	21	21	56	..	..	21	42	0
	B	0	14	0	35	0	35	0	35	0	21	0	18	0	14	..	14
18	A	7	..	21	..	..	..	7	..	7	..	..	..	7	..	7	..
	B	0	28	21	28	28	..	21	28	14	..	14	..	..	..	..	..
	C	14	..	14	..	28	..	7	..	7	..	..	..	7	..	7	..
19	A	14	35	14	49	14	35	..	..	..	49	14	..	14	35	14	..
	B	7	7	14	14	21	28	21	28	..	28	..	28	..	28	..	28
20	A	21	0	21	0	35	..	35	4	..	0	..	0	..	0	..	0
	B	28	7	35	7	35	7	42	21	..	..	..	..	39	..	..	..
21	A	14	7	14	7	42	21	42	7	..	..	42	7	28	7	42	7
	B	..	0	..	4	..	..	..	..	..	11	..	11	..	..	..	11
22	A	0	42	11	28	..	..	18	28	11	21	0	..	0	21	..	14
23	A	0	56	14	56	21	42	14	28	4	28	4	28	..	21	4	21
24	A	14	56	42	..	21	42	7	..	..	21	7	11	0	11	..	11
Average.....		10	17	17	19	20	19	16	12	11	15	17	11	11	13	10	8
Range.....		0-35	0-56	0-49	0-56	0-56	0-42	0-60	0-35	0-49	0-49	0-60	0-35	0-39	0-35	0-42	0-28

* These increases are determined on the basis of a percentile increase over an initial control level, measured in terms of gram calories per second per square centimeter of skin surface.

† In this table, MS is used to designate morphine sulfate, and MAM, monoacetylmorphine.

only 8 per cent. In spite of the wide individual variations, there was absence of an appreciable response to the use of monoacetylmorphine in 1 subject only—subject 3, who was 1 of the 2 subjects who had shown a similar lack of response to the use of morphine sulfate.

The same reasons that made accurate measurement of reaction to pain impossible in the tests with morphine sulfate applied to experiments with monoacetylmorphine. In general, however, no greater increases in the spread between perception of pain and reaction to pain were noted after the use of the latter drug than after the former.



The curves represent average values obtained in studying a group of 20 normal persons. The time intervals (abscissa) represent the number of minutes after the subcutaneous administration of a standard dose of morphine sulfate (broken line) or of monoacetylmorphine hydrochloride (solid line). Ordinate values represent the percentage increases in threshold of pain perception above the initial control figure determined for each subject and expressed as zero.

Comparison of the average curves representing the threshold-raising effects of the two drugs (chart 1) indicates a slight, if any, difference between them. Apparently, the given dose of morphine sulfate (0.24 mg. per kilogram of body weight) consistently had a slightly greater analgesic property than freshly prepared aqueous solutions of monoacetylmorphine in doses of one-fourth the amount by weight. It should be pointed out, however, that the difference was not greatly in excess of the error inherent in the method employed.

B. Pain Due to Muscular Ischemia.—In the 13 subjects tested by the method described, severe aching pain in the forearm was produced consistently. This pain was continuous throughout the experiment and increased in intensity after each interval of muscular contraction. The blood pressure readings during the periods in which pain was produced were all elevated. The average increase over the normal systolic pressure was 23 per cent, and that over the normal diastolic pressure, 28 per cent. Detailed readings of the blood pressure with individual variations are shown in table 2.

From the results of the experiments on cutaneous pain due to heat radiation it was obvious that an appreciable analgesic effect of monoacetylmorphine could be expected within thirty to sixty minutes after administration of the drug. Accordingly, forty-five minutes after the injection its effects were measured by repetition of the entire test. Twelve of the 13 subjects noted that, although pain was still present, its intensity was distinctly diminished throughout the period during which vascular occlusion was maintained. The accuracy of this observation was confirmed by the absence of any motor withdrawal or struggling, which had been present uniformly during the control experiment. In spite of this definite diminution of pain following the use of the drug, the elevation of blood pressure during the production of pain did not differ appreciably from that previously noted—the average maximum elevation of systolic pressure being 23 per cent for the entire group and the maximum increase in diastolic pressure being 27 per cent. Another interesting point was the subjective impression obtained by practically all the subjects that the test performed after the administration of monoacetylmorphine covered a much shorter period than the initial test. When asked to state specifically how the time taken by the two tests compared, the subjects answered that the experiment following the drug was one-fourth to one-half as long as the control experiment. Certain subjects described the pain as being sharply localized in the middle of the forearm, as compared with its presence over the entire forearm, and sometimes the hand as well, when no drug was administered. As had been noted in the tests on cutaneous pain due to heat radiation the 1 subject who failed to respond to the administration of either morphine sulfate or monoacetylmorphine again failed in the muscular ischemia test to demonstrate any subjective or objective change in sensitivity to pain following the injection of monoacetylmorphine. In over half the subjects, the total number of muscular contractions of the hand and fore-

arm during the period of production of pain was materially increased after the administration of the drug as compared with the number recorded in the control experiments.

Side Reactions to Drugs (table 3).—Almost without exception, during the course of the of 24 subjects. After the injection of monoacetylmorphine, only 1 subject had vomiting, and only 7 complained of nausea. Vomiting was precipitated apparently in practically every instance by the subject's attempt to walk. The other side reactions noted after the administration of mor-

TABLE 2.—*Results of the Arm Ischemia Test Before and After Use of Monoacetylmorphine*

Subject Number	Number of Contractions: First Period, Before Drug	First Period, After Drug	Second Period, Before Drug	Second Period, After Drug	Third Period, Before Drug	Third Period, After Drug	Blood Pressure Before Pain	Changes in Blood Pressure: Percentile Systolic Rise, Before Drug	Percentile Systolic Rise, After Drug	Percentile Diastolic Rise, Before Drug	Percentile Diastolic Rise, After Drug
1	65	105	20	25	5	—	110/75	30	24	32	29
2	100	120	8	7	3	3	105/60	26	32	29	30
3	59	40	5	12	0	6	125/75	22	20	24	23
4	48	40	4	30	0	30	120/85	24	16	29	26
5	76	135	40	11	8	0	115/75	14	20	31	25
6	114	140	15	20	12	15	110/60	23	23	40	40
7	73	115	40	34	23	42	120/60	22	23	30	30
8	60	85	16	17	12	..	115/70	35	28	30	29
9	80	100	20	35	35	..	125/70	24	29	32	30
10	88	...	30	55	..	61	110/70	27	23	30	27
11	130	178	21	65	16	88	120/75	26	20	30	25
12	110	100	60	40	30	20	120/75	13	21	25	18
13	90	...	100	60	0	0	130/80	14	21	20	20
Average no. contractions..	84	105	26	36	11	20	Average rise	23	23	28	27

TABLE 3.—*Side Reactions Following Use of Morphine Sulfate and Monoacetylmorphine* *

Subject No.	Nausea: MS	Nausea: MAM	Vomiting: MS	Vomiting: MAM	Depression: MS	Depression: MAM	Elation: MS	Elation: MAM	Itching: MS	Itching: MAM	Pallor: MS	Pallor: MAM	Sweating: MS	Sweating: MAM	Sleepiness: MS	Sleepiness: MAM	Thirst: MS	Thirst: MAM	Dizziness: MS	Dizziness: MAM
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—
2	+	—	+	—	+	—	—	—	+	+	+	+	—	—	+	—	+	+	+	—
3	+	—	+	—	+	—	—	—	+	—	+	+	—	—	+	—	+	+	+	—
4	+	+	+	—	+	—	—	+	+	+	+	+	+	+	+	+	+	—	+	—
5	+	—	+	—	+	—	—	—	+	+	+	+	+	—	+	—	+	—	+	—
6	+	+	+	—	+	—	—	+	+	—	++	+	+	—	+	—	+	—	+	—
7	+	—	+	—	—	—	—	—	—	—	+	—	—	—	+	—+	+	—	+	+
8	+	+	+	+	+	—	—	—	—	+	+	+	+	+	+	+	+	+	+	—
9	+	+	+	—	+	—	—	+	+	—	+	+	+	—	+	+	+	—	—	—
10	+	—	+	—	+	—	—	—	+	—	+	+	+	—	+	+	+	—	+	—
11	+	—	—	—	+	—	—	+	+	—	+	+	+	—	+	—	+	—	+	—
12	—	—	—	—	—	—	+	+	+	+	+	+	—	—	+	—	+	—	—	—
13	—	—	—	—	—	—	—	+	+	+	+	+	+	—	+	—	+	—	+	—
14	+	+	+	—	+	—	—	—	+	+	+	—	+	—	+	—	+	—	+	—
15	+	—	+	—	+	+	—	+	+	+	+	+	+	+	+	—	+	+	+	—
16	+	—	+	—	+	—	—	—	+	—	+	+	+	—	+	—	+	—	+	—
17	+	+	+	—	—	—	—	—	—	—	+	—	+	—	+	—	+	—	—	—
18	+	—	+	—	+	—	+	++	+	—	+	+	+	—	+	+	+	—	+	—
19	+	—	+	—	—	—	—	—	+	+	+	—	—	—	+	—	+	—	—	—
20	+	—	+	—	—	—	—	—	+	—	—	—	—	—	+	—	+	—	—	—
21	+	—	+	—	—	—	—	—	+	—	+	—	—	—	+	+	+	+	+	—
22	+	—	+	—	+	+	—	—	+	+	+	+	—	—	+	+	+	—	+	+
23	+	+	+	—	—	—	—	—	—	+	+	+	+	+	+	+	+	—	+	+
24	+	—	+	—	—	—	—	—	+	+	+	+	—	—	+	+	+	—	+	+
Total subjects	21	7	20	1	14	1	2	8	19	12	22	17	15	4	23	10	23	5	19	4

* MS indicates morphine sulfate; MAM, monoacetylmorphine; +, presence of side reaction, and —, absence of side reaction.

experiments it was noted that the side reactions associated with the use of monoacetylmorphine were less striking than those observed after the injection of morphine sulfate. After injection of the latter drug, the most disagreeable reaction was nausea and vomiting, which occurred in 21

phine sulfate, in their order of frequency, were thirst, sleepiness, pallor, dizziness, itching and sweating, and in 1 instance a state of euphoria. After the injection of monoacetylmorphine, dizziness was only occasionally observed, being much less apparent than that resulting from morphine

sulfate; pallor and sweating, though experienced, were much less intense; itching (generalized or localized to the nose) was present in about the same degree. A state of euphoria, a striking sense of well-being and mental exhilaration, however, was evident in 8 subjects after administration of monoacetylmorphine, as compared with its presence in 1 subject after injection of morphine sulfate. In general it can be stated that essentially no unpleasant effects were noted after the use of monoacetylmorphine.

COMMENT

The results of the studies on cutaneous pain due to heat radiation indicate that in the dose used morphine sulfate was only slightly, if at all, more effective in its analgesic properties than monoacetylmorphine, the difference observed being little greater than the error inherent in the method. The similarity of the two drugs in their effect on elevation of the threshold of pain perception was equally apparent throughout the four hour period of the test, although the dose by weight of morphine sulfate was approximately four times that of monoacetylmorphine. There was little difference, either, in the effect of the two drugs on the threshold of reaction to pain, as measured by the level at which wincing occurred. As previously observed, 2 subjects obtained no analgesic effect whatever from morphine sulfate, and 1 of the 2 subjects also failed to show any demonstrable response to monoacetylmorphine when pain was tested by production of muscular ischemia.

The results of our experiments following the use of morphine sulfate are of interest as compared with the conclusions of Wolff and his collaborators,[6] who used essentially the same dose of the drug. The shape of the curve, indicating a rise in the threshold of pain perception after the administration of morphine (chart), was similar to that obtained by Wolff, but his maximum percental increase was much greater than ours. This discrepancy may be due to a difference in the quality of the sensation which was taken as the beginning of pain perception by the two laboratories. Slaughter,[7] in similar studies with morphine sulfate, obtained changes of the same magnitude of elevation of threshold, with regard to maximum effect and duration of action, as those we obtained.

6. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies on Pain: Measurement of the Effect of Morphine, Codeine, and Other Opiates on the Pain Threshold and an Analysis of Their Relation to the Pain Experience, J. Clin. Investigation **19**:659-680, 1940. Hardy and associates.[2]

7. Slaughter, D.: Personal communication to the authors.

The clinical significance of the magnitude of the elevation of the threshold of pain perception produced by the use of these two drugs is not clearly understood. It is of interest to note that in current studies being made on the effect of inhalation of nitrous oxide on perception of pain, a subject who had shown an elevation in the threshold of pain perception of 18 per cent after the use of morphine sulfate and of monoacetylmorphine, in the doses employed in this study, had an elevation of 20 per cent after the inhalation of a 50 per cent mixture of nitrous oxide and oxygen. Shortly after this change in threshold following the inhalation of nitrous oxide had been recorded, the subject lost consciousness. For a proper evaluation of this result, it is to be recalled that mixtures containing nitrous oxide in 50 per cent concentration are used routinely for relief of labor pains, a fact which offers indirect evidence of the clinical significance to be attached to the degree of elevation of the threshold of pain following the use of the analgesic drugs employed in the present study.

The striking reduction in pain resulting from muscular contraction in the presence of complete vascular occlusion produced by the use of monoacetylmorphine is in entire agreement with the observations on pain produced by heat radiation. An important difference in the types of pain produced by the two methods deserves comment, however. The pain produced by muscular contraction in the presence of muscular ischemia is a sustained type, more comparable to pain observed clinically than that produced by single, short periods of cutaneous stimulation by intense heat. In the experiments on muscular ischemia it was frequently observed that the use of monoacetylmorphine permitted the subject to contract his fist for longer periods than was previously possible without the use of the drug. Since in this experiment both pain and fatigue contribute to the subject's inability to perform continued muscular contractions, it is readily conceivable that the administration of monoacetylmorphine might, in addition to its analgesic effect, appreciably prolong the ability to continue muscular effort. Such an effect would be of extreme importance in instances in which it is necessary to move wounded or traumatized patients over great distances.

A further suggestion that the use of monoacetylmorphine may be preferable to that of morphine sulfate with ambulatory patients suffering from painful lesions is to be found in the fact that with the former drug not only were few important side reactions encountered but a state of moderate euphoria was frequently associated with its analgesic action. The stimu-

lating effect might be a deciding factor in enabling the patient voluntarily to cooperate in his mobilization. On the other hand, the very absence of side effects makes the possibility of addiction to monoacetylmorphine greater than that to morphine sulfate, and this fact is emphasized. Although studies on the possible deterioration of monoacetylmorphine in aqueous solution are not conclusive, our observations suggest the need for careful study of the physical properties of the drug under varying conditions of temperature, solution and the like.

SUMMARY

1. Comparative studies on a group of 24 normal subjects on the analgesic effects of morphine sulfate and of monoacetylmorphine on cutaneous pain produced by the heat radiation method of Wolff and Hardy and on muscular pain produced by muscular exercise under conditions of complete vascular occlusion of an extremity (muscular ischemia) indicate that a given dose of monoacetylmorphine is about four times as effective as a similar dose of morphine sulfate in control of pain, as regards both the maximum elevation of threshold obtained and the duration of its action.

2. The side reactions incident to the use of monoacetylmorphine are distinctly less than those associated with the administration of morphine sulfate. This is particularly true with regard to the occurrence of nausea and vomiting.

3. The use of monoacetylmorphine, in addition to its analgesic effect, appears to permit increased voluntary muscular effort in the presence of severe pain, as evidenced by the experiments with muscular ischemia.

4. Notable individual variations occurred in the responses to each of the drugs employed. Two subjects obtained no measurable analgesic effect from morphine sulfate and relatively little from monoacetylmorphine.

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POSTOPERATIVE THROMBOCYTOSIS

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Among experimental and clinical measures which are reported to raise the platelet count, surgical procedures, particularly splenectomy, have attracted much attention. This phenomenon is of interest for at least two reasons: First, the rise in the platelet count is more difficult to rationalize than many of the other thrombocytoses, such as those related to primary augmentation of the function of the bone marrow; second, the association of platelets with the clotting process has led to the loosely formulated belief that their increase after a surgical operation is connected with the occurrence of postoperative thrombosis.

The first extensive clinical investigation of this subject to be reported was that of Hueck [1] in 1925 who studied 100 varied surgical patients and found a brief fall in the platelet count postoperatively, followed by a rise to as much as three times the normal preoperative level. Hueck found the rise to begin at about the seventh postoperative day and the count to return to the preoperative level by two weeks after operation. Dawbarn, Earlam and Evans [2] made one of the most comprehensive studies reported in English. Fifty patients were found to show a substantial rise in platelets after operation, the maximal values being reached on the tenth postoperative day. The authors were impressed by a general correlation between the extent of the operation and the degree of increase in platelets and suggested that the elevation might be related to the reabsorption of necrotic tissue.

A number of corroborative papers have since appeared, among them those of Normann,[3] König [4] and Gradwohl and Hiller.[5] A single study of the platelet volume postoperatively [6] indicated that there is actually more circulating platelet material and answered the question as to whether the rise represents merely an increase in the amount of platelet fragmentation. Experimental animals have yielded approximately the same results as human patients. Several investigators have demonstrated a moderate but significant rise in the rabbit.[7]

The observation of a postoperative and posttraumatic rise in the platelet count has not gone unchallenged. Allen [8] in 1927 was unable to discover any variation from normal in 12 patients followed postoperatively; details of counting technic and length of follow-up were not presented. Fisher [9] likewise reported no significant changes in the counts of 6 patients after operation, but he pointed out that these persons were followed for only six days each. The most formidable negative report is a recent one by Potts and Pearl.[10] In a group of 52 patients who had had major operations, they found only minimal changes consisting in an average rise of 9 per cent above the preoperative level of platelets.

The thrombocytosis occurring after splenectomy is accepted more universally than that re-

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1. Hueck: Blutplättchenveränderungen nach Operationen, München. med. Wchnschr. **73**:173, 1925.

2. Dawbarn, R. T.; Earlam, F., and Evans, W. H.: Relation of Blood Platelets to Thrombosis After Parturition and Pregnancy, J. Path. & Bact. **31**:833, 1928.

3. Normann, E.: Wie verhalten sich die Thrombocyten nach operative behandelten Krankheitsfallen und bie der Entstehung postoperative Thrombose? Deutsche Ztschr. f. Chir. **212**:166, 1928.

4. König, W.: Experimentelle Untersuchungen über die Entstehung der Thrombose, Arch. f. klin. Chir. **171**:447, 1932.

5. Gradwohl, R., and Hiller, S. T.: Blood Platelet Count in Postoperative Thrombosis, J. Mississippi M. A. **31**:392, 1934.

6. Evans, W. I., and Fowler, W. M.: Effect of Splenectomy and Other Operations on Platelets as Determined Volumetrically, Proc. Soc. Exper. Biol. & Med. **32**:512, 1934.

7. Bachman, E. L., and Hultgren, G.: Influence de l'intervention chirurgicale sur la teneur du sang en thrombocytes, Compt. rend. Soc. de biol. **94**:942, 1926. Liles, R. T.: Blood Platelets in Rabbits Following Splenectomy and Transplantation of Spleen, Proc. Soc. Exper. Biol. & Med. **23**:489, 1926. Steiner, P. E., and Gunn, F. D.: Effect of Splenectomy and Other Surgical Procedures upon Circulating Blood Platelets, ibid. **28**:1088, 1931.

8. Allen, E. V.: Changes in the Blood Following Operation, Arch. Surg. **15**:254 (Aug.) 1927.

9. Fisher, L. C.: Platelet Count After Splenectomy and Other Operations, Proc. Soc. Exper. Biol. & Med. **29**:316, 1931.

10. Potts, W. J., and Pearl, E.: Platelet Count and Coagulation Time of Plasma and Whole Blood Postoperatively, Surg., Gynec. & Obst. **73**:492, 1941.

ported to follow other types of operation. The highest platelet counts encountered are those for splenectomized patients,[11] and it is recognized that these high levels may be maintained for many months following operation.[12] The rise occurring after splenectomy is found in a variety of diseases involving the spleen, as well as after removal of the normal traumatically ruptured spleen.[13] While the cause of the thrombocytosis which occurs after other operations is poorly understood, it is believed that after splenectomy increases in platelets are due, at least in part, to the removal of the normal thrombolytic activity of that portion of the reticuloendothelial system.[13b] Bedson[14] offers some experimental corroboration of this view.

Although the occurrence of a postoperative thrombocytosis seems fairly well established, many of the confirmatory studies are based on varied and poorly controlled methods of counting. In addition, as previously mentioned, there are several negative reports in the literature. Therefore, it is worth while to report some observations on a group of surgical patients with a simple direct venous platelet-counting method, the advantages of which have been discussed by Tocantins.[15]

METHODS

After several different counting methods had been tried, a method essentially that of Nygaard[16] was found most satisfactory. This is a direct plasma platelet count which has many of the advantages of Thomsen's[17] technic but escapes the disadvantage of requiring a hematocrit determination.

The materials required include a 10 cc. syringe calibrated in single cubic centimeters; 50 cc. contrifuge tubes; a sterile 1.1 per cent solution of sodium oxalate, an unsterile refrigerated 1.1 per cent solution of sodium oxalate, and uncalibrated capillary pipets.

Through a 20 gage needle, a 10 cc. syringe is carefully filled with sterile 1.1 per cent sodium oxalate solution exactly to the 9 cc. mark. A venipuncture is done with minimal trauma, and with light or no stasis. If stasis is used, the tourniquet should be released as soon as the vein is entered, and five seconds should elapse before the blood is withdrawn. Blood is then removed until exactly 1 cc. has been taken—i. e., the plunger of the syringe is at the 10 cc. mark. The resultant blood-oxalate mixture is placed in a clean dry 50 cc. centrifuge tube, and with the same syringe and needle an additional 30 cc. of 1.1 per cent sodium oxalate solution, which need not be sterile, is transferred to the centrifuge tube, so as to make a resultant 1 : 40 dilution of the original 1 cc. of blood. This is now mixed by inverting, and then the centrifuge tube is capped to prevent evaporation and is placed upright in a cool place to await sedimentation of the red and white cells. When a narrow but definite bank of clear plasma-oxalate has appeared at the top of the fluid (usually one to two hours), a small amount of this overlying oxalated plasma is taken up in a clean dry capillary pipet and placed in both sides of a counting chamber.[18] After at least ten minutes is allowed for the platelets to settle, the count is made with the high dry lens (400 diameters) under reduced light. The field seen is almost free of red and white cells and contains chiefly platelets. These appear typically as small (2 to 5 micron), sharply defined bodies, which are either highly refractile or dark, depending on the clearness of focus. They are usually globular but may present long processes or irregular shapes, as noted by many observers.[19] Ten small squares are counted for each determination, five on each side of the chamber, as for a red cell count, and the result multiplied by the dilution factor of 1,000 (blood dilution 1:40; 0.04 cu. mm. of blood counted in ten small squares) to give the number of platelets per cubic millimeter of whole blood.

In Thomsen's method, the error made by counting platelets in virtually cell-free oxalated plasma and then calculating them for whole blood is a considerable one, which requires correction by the hematocrit reading. With the

11. Tocantins, L. M.: The Mammalian Blood Platelet in Health and Disease, Medicine **17**:155, 1938.

12. Galloway, J. F.: Blood Platelets After Splenectomy, Lancet **2**:1235, 1931.

13. (*a*) Woolstein, M., and Kreidel, K.: Blood Picture After Splenectomy in Children, Am. J. Dis. Child. **51**:765 (April) 1936. (*b*) Krumbhaar, E. B.: Changes Produced in Blood Picture by Removal of Normal Mammalian Spleen, Am. J. M. Sc. **184**:215, 1932. (*c*) Evans, W. H.: Blood Changes After Splenectomy, J. Path. & Bact. **31**:815, 1928.

14. Bedson, S. P.: Effect of Splenectomy on Experimental Purpura, Lancet **2**:1117, 1924.

15. Tocantins, L. M.: Technical Methods for the Study of Blood Platelets, Arch. Path. **23**:850 (June) 1937.

16. Nygaard, K. K.: Direct Method of Counting Platelets in Oxalated Plasma, Proc. Staff Meet., Mayo Clin. **8**:365, 1933.

17. Thomsen, O.: A Method for the Direct Count of Blood Plates in the Blood, Acta med. Scandinav. **53**:507, 1920.

18. Levy-Hausser dark line chambers were used throughout.

19. Ferguson, J. H.: Observations on the Alterations of Blood Platelets as a Factor in the Coagulation of the Blood, Am. J. Physiol. **108**:670, 1934.

high dilution of blood employed in the present method, however, this error becomes negligible. Nygaard [16] calculates that even with a hematocrit reading of 75 per cent only 3.75 per cent need be subtracted from the platelet count made in a final blood-oxalate dilution of 1:20. With a 1:40 dilution, as was employed in the counts to be reported, the error is much smaller.

The presence of bacteria, which resemble platelets in the counting chamber and may therefore artificially raise the count, is avoided by employing only diluting fluid that is either sterile or refrigerated. Repeated blank counts on the unsterile diluting fluid alone have never shown the presence of more than 5 to 10 platelet-like bodies in the total area examined.

Still another factor must be considered in a method which depends on differential sedimentation of the red cells and the platelets: the magnitude of the factor of loss of platelets from the overlying suspension by sedimentation and by adhesiveness to the glass walls of the container. Trials were made of the suspension stability of platelets in preparations identical with those used for the counts reported. Blood was taken from 2 ostensibly normal persons and from 2 postoperative patients with elevated platelet counts. Serial counts were made on each of these specimens over a period of twenty-four hours, samples being aspirated from three different levels of each preparation (top, middle and bottom of the clear overlying layer) at the end of each time interval. These platelet suspensions were found to be stable for at least six hours, and within this period the counts made on them did not vary significantly with time or region.

Since paraffined tubes were not routinely used, adhesiveness of platelets—chiefly to the glass walls of the container—was another possible source of error. Wright [20] showed that the magnitude of this error could be considerable and that the degree of loss of platelets from solutions by this route varied inversely with the concentration of anticoagulant used. In an attempt to evaluate this factor, preparations exactly like those used for counting were centrifuged at 1,600 revolutions per minute for one minute and samples of the platelet-rich supernatant were placed in each of two test tubes, one paraffined and the other plain. These tubes were slowly rotated, and platelet counts were made on samples from them at short intervals. It was found for both a normal subject and a postoperative patient that no significant drop in the number of platelets occurred during the first two hours and that there was no appreciable difference in this period between the concentration of platelets in the paraffined and that in the nonparaffined tube. The disparity between these results and those of Wright is probably ascribable to the much higher concentration of anticoagulant used for the diluting fluid in the present studies, as well as to the use of greatly diluted plasma.

Preoperative and Maximum Postoperative Platelet Counts in a Sample Group of Patients

Patient	Name	Sex	Age	Operation	Last Preoperative Count Platelets per C.Mm.	Maximum Postoperative Count Platelets per C.Mm.	Post-operative Day (Maximum Count)	Per Cent Rise
1	J. C.	M	83	Hip pinning	314,000	393,000	11	25
2	I. V.	M	23	Laminectomy	387,000	817,000	9	110
4	M. V.	F	43	Herniorrhaphy	277,000	605,000	6	118
5	C. M.	M	71	Nephrectomy	522,000	841,000	16	61
6	A. M.	M	74	Prostatectomy	241,000	384,000	8	59
7	F. G.	M	35	Midthigh amputation	293,000	562,000	11	91
11	E. M.	M	24	Laparotomy	464,000	608,000	6	28
12	G. P.	F	56	Laparotomy	496,000	711,000	6	42
13	M. B.	F	66	Resection of colon	464,000	538,000	13	16
14	A. K.	F	55	Cholecystectomy	422,000	671,000	20	59
34	J. W.	M	54	Midthigh amputation	382,000	654,000	12	72
39	S. H.	M	45	Herniorrhaphy	325,000	397,000	10	22
16	C. M.	M	42	Splenectomy	113,000	1,800,000	11	1,470
18	W. T.	M	23	Splenectomy	348,000	1,489,000	11	328

A final test of the method, and the most realistic one, was a series of six sets of duplicate counts made for the same persons at the same time. When blood was withdrawn from each of the two arms and prepared and examined for platelets separately, the average discrepancy in the two counts of each set was only 6 per cent.

RESULTS

1. Normal Counts.—Platelet counts were made for 36 ostensibly normal young persons, including nurses, medical students and patients hos-

20. Wright, H. P.: The Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anti-Coagulants, J. Path. & Bact. **53**:255, 1941.

pitalized for functional psychiatric disorders. The average of these counts was 322,000 per cubic millimeter, with a range of from 236,000 to 445,000. It is of interest that the average of these 36 counts is approximately the same as Nygaard's average for a much larger series of normal counts, "about 320,000 per cubic millimeter." [16]

2. Preoperative Counts.—Preoperative counts were made for 63 varied surgical patients, many of whom were subsequently followed postoperatively. The average for this group was 365,000

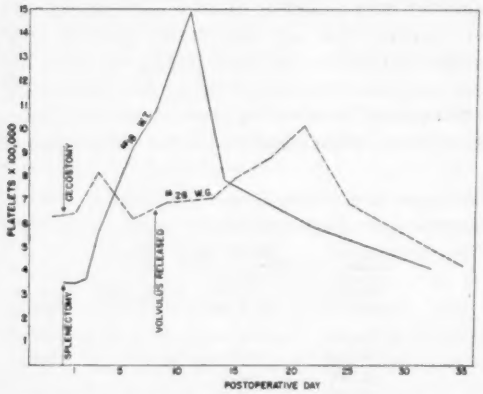

Chart 1.—Individual examples of postoperative platelet changes.

per cubic millimeter. The difference between this and the normal average, if significant, can perhaps be ascribed to the presence among the preoperative group of chronic infections and other disorders known to elevate the platelet count. Serial counts on alternate days were done preoperatively for a number of these persons for variable periods up to a month without the appearance of any large fluctuations in the preoperative level of platelets.

3. Postoperative Counts.—Forty-one patients chosen at random were followed postoperatively for periods ranging from eight to thirty-six days. These patients were suffering from various disorders and underwent varied types of operations, including splenectomy. In the table are shown the degree and the time of occurrence of the maximum postoperative rise in a sample group of the subjects followed, since space does not permit detailed presentation of these data for the entire group. The percentage rise is calculated on the basis of the last preoperative count as 100 per cent. For most patients only one preoperative count was done; the remaining ones had no preoperative counts significantly or consistently higher than the final count preceding operation. Charts 1 and 2 show graphically the time relations and the extent of the changes in platelet level for several of the patients followed. Chart 3 is a graphic summary of the complete data presenting the averaged absolute counts and percentage differences throughout the period that patients were followed. The values for the average platelet count of the normal group and those of the preoperative group are superimposed for comparison in the lower half of chart 3, while in the upper half the percentage values of the average platelet count at the various days are calculated on the basis of the final preoperative count as 100 per cent.

In evaluating the series of postoperative platelet counts, one is faced with a number of complexities. It is clear that there are many factors in surgical procedures beyond the mere operative onslaught, all of which may have a profound effect on the platelet count. These patients presented different disease pictures originally, underwent operations of varying type and extent and lost variable amounts of blood. Some were given transfusions before and after operation and some received sulfonamide compounds as well as other drugs before and after operation. In addition, a number of the patients had various postoperative febrile complications, such as pneumonia, infection of the wound or infection of the urinary tract. These varied factors might be expected to have some effect on the concentration of platelets in the peripheral circulation. At present, however, there is no way of eliminating these variables, which will no doubt be found in any group of surgical patients. Hence one can only neglect them, after calling attention to their presence.

Excluding the 2 splenectomized patients from consideration, 22 of the 39 remaining patients

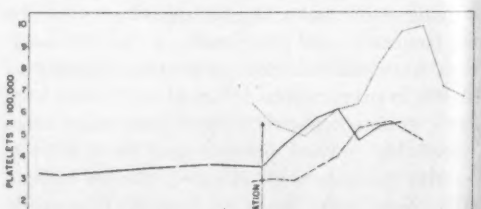

Chart 2.—Individual examples of postoperative platelet changes. The line of short dashes represents case 8 (abdominoperineal resection); the solid line, case 15 (sigmoid resection), and the line of longer dashes, case 21 (nephrolithotomy).

had a postoperative rise of platelets amounting to more than twice the standard deviation of the group of preoperative counts (105,000 per cubic millimeter). This degree of increase is taken

conservatively to be significant, although inspection of the individual protocols suggests a greater incidence of significant elevations.

In charts 1 and 2 are shown several representative individual platelet responses to operations. Among the most convincing are those of patients who had two separate operations, each succeeded by a distinct rise in the platelet count. Case 28 exemplifies this: Cecostomy was followed by an immediate and rapidly receding increment in the platelet count. A volvulus then developed, requiring immediate operation on the fourteenth day after cecostomy, when the platelet count had already returned to its preoperative level. After this incident, a higher, more sustained elevation occurred, with a peak at slightly over 1,000,000 per cubic millimeter. Thirty-five days postoperatively the count had reached an approximately normal level. Case 21 is charted because it is a typical example of the postoperative change in the platelet count, with its peak between the

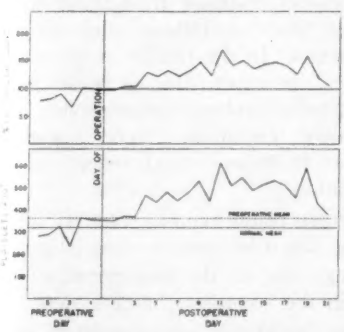

Chart 3.—Average absolute and percentage rise in the platelet count of 41 patients following operation.

tenth and the fifteenth day. Case 15 demonstrates the relative constancy of serial preoperative counts for these patients, which was noted for most, but not all, of the persons followed. The platelet response in case 18 is rather typical of that following splenectomy, as reported by other investigators previously mentioned. Case 8 demonstrates that a substantial rise in platelets may occur postoperatively even though the preoperative level of platelets is already much elevated.

These data support the conclusion that a significant rise in the level of blood platelets occurs postoperatively but that it is a variable one, ranging from 30 per cent to more than 100 per cent above the preoperative level. It seems equally true that this phenomenon is not demonstrable in every case.

The time relations of the maximal rise are likewise variable. The period from the seventh to the twentieth postoperative day includes the great majority of the individual peaks, and these are most frequent in the interval between the tenth and the fourteenth day inclusive—an observation in substantial agreement with the results of previous investigators. The maximal platelet counts of the subjects in this study, however, occurred anywhere from the day of operation to the twenty-first postoperative day.

COMMENT

Postoperative thrombocytosis is difficult of explanation, in part because the rise following operation is so long delayed (eight to fifteen days). The hypothesis generally offered is that it is in some manner dependent on absorption from the wound of necrotic material, exudate, etc., a point of view which is supported by certain experimental observations. König [4] and Zschau,[21] for example, demonstrated a similar rise in platelets after the parenteral administration of isogenous tissue extracts and the implantation of autogenous muscle grafts in animals. Pohle [22] likewise suggested that the periodic postmenstrual rise in platelets in normal women may be due to the absorption of necrotic endometrium. Moreover, Dawbarn, Earlam and Evans [2] explained the increase in platelets during convalescence from pneumonia on the basis of absorption of the resolving exudate. An alternative hypothesis was originally suggested by Hayem: [23] that the thrombocytosis is an overcompensatory response to the initial thrombopenia noted both in immediate postoperative periods and during acute infections.

The etiologic significance of postoperative thrombocytosis in the occurrence of clinical thrombosis is a problem which requires much clarification. Platelets are believed to function in blood coagulation by virtue of two fundamental mechanisms: (1) the release of thromboplastin in initiating the plasma clotting process and (2) agglutination, either reversible or irreversible, to each other and to vascular endothelium. These functions are distinctly separated in lower forms, such as Limulus,[24] and may be experimentally separated in the mammal by the use of heparin.[25] The importance

21. Zschau, H.: Untersuchungen zur Thrombosefrage, Deutsches Arch. f. klin. Chir. **230**:13, 1931.

22. Pohle, F. J.: Blood Platelet Count in Relation to Menstrual Cycle in Normal Women, Am. J. M. Sc. **197**:40, 1939.

23. Hayem, G.: De la crise hématique dans les maladies aigues à défervescence brusque, Compt. rend. Acad. d. sc. **94**:200, 1882.

24. Loeb, L.: Amoeboid Movement and Agglutination in Amoebocytes of Limulus, Protoplasma **2**:572, 1927.

25. Solandt, D. Y., and Best, C. H.: Time Relations of Heparin Action on Blood Clotting and Platelet Agglutination, Lancet **1**:1942, 1940.

of either or both together (as interdependent events in clotting) in initiating clinical thrombosis has not been assessed; nor is it known whether a tendency toward intravascular clotting by either mechanism is significantly enhanced by the mere presence of a greater number of circulating platelets. In fact, it would seem that, while the clotting of plasma is appreciably slowed by marked reduction in the number of contained platelets, yet even a great increment in their concentration has no effect in the reverse direction of accelerating clotting.[26] The purely agglutinative properties of platelets acquire more interest, however, in the light of the present belief that antemortem thrombi are first formed from agglutinated platelets[27] and that the red portions of the clot are formed only later from all the elements of the circulating blood.

Functional changes in platelets postoperatively have been examined in a number of ways in recent years. The agglutinability of platelets has been found to be enhanced in the presence of clinical thrombosis[28] and postoperatively.[29] The adhesiveness of blood platelets, measured by a simple method, has recently been shown to increase postoperatively, paralleling the postoperative thrombocytosis.[30] A decrease in the resistance of platelets to hypertonic solutions has also been noted in the thrombocytoses occurring after infections and after operations.[31]

Satisfactory empiric evidence that thrombocytosis increases the chances of thrombosis, however, is so far lacking. While peripheral and mesenteric thromboses are not infrequent after splenectomy for splenic anemia,[32] they do not occur so commonly after splenectomy for other conditions, although operations of the latter type are followed by an equally pronounced thrombocytosis.[33] Fatal thromboses have been often reported in the presence of a normal or subnormal platelet count,[34] while there are numerous instances of extremely high counts uncomplicated by evidence of thrombosis.[34b]

Although the series here studied is admittedly small, the data presented seem neither to support clearly nor to argue against the tissue-trauma hypothesis of postoperative thrombocytosis. It is true that inspection of the data shows a rough correlation between the extent of operation and the degree and maintenance of the postoperative elevation. The patients subjected to major abdominal operations involving a good deal of dissection and manipulation clearly showed a greater platelet response than those who were recovering from operations such as subtotal thyroidectomy. In the middle range of surgical procedures, however—the perineal prostatectomies, herniorrhaphies, laparotomies, etc.—the postoperative elevations were variable and seemed not to depend closely on the severity of the operation.

Differential platelet counts were not attempted, but it was noted incidentally that in many cases the average size of the postoperative platelets, as seen in the counting chamber, was reduced, sometimes strikingly so, compared with the same patient's platelets preoperatively. The possible significance of this fact has been discussed by Olef.[35]

In only 1 patient did a serious thromboembolic accident complicate the postoperative course. This occurred in a 72 year old man who was operated on for carcinoma of the rectosigmoid. Three days before operation the platelet count was 1,221,000 per cubic millimeter. It rose to 1,489,000 on the evening of the day of operation and fell to approximately 1,000,000 on the fourth postoperative day. On the fifth day the patient died suddenly of the effects of a

26. Eagle, H.: Studies on Blood Coagulation: Role of Prothrombin and of Platelets in the Formation of Thrombi, J. Gen. Physiol. **18**:531, 1935. Nygaard, K. K.: Hemorrhagic Diseases, St. Louis, C. V. Mosby Company, 1941.

27. Bizzozero, J.: Ueber einen neuen Formbestandteil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung, Virchows Arch. f. path. Anat. **90**: 261, 1882. Welch, W. H.: The Structure of White Thrombi, in Papers and Addresses, Baltimore, Johns Hopkins Press, 1920, vol. 1, p. 47. Shionoya, T.: Studies in Experimental Extracorporeal Thrombosis, J. Exper. Med. **46**:18, 1927. Best, C. H.; Cowan, C., and Maclean, D. L.: Heparin and the Formation of White Thrombi, J. Physiol. **92**:20, 1938.

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29. Heusser, H.: Postoperative Blutveränderungen und ihre Bedeutung für die Entstehung der Thrombose, Deutsche Ztschr. f. Chir. **210**:132, 1928. Jürgens, R., and Naumann, W.: Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, Deutsches Arch. f. klin. Med. **172**:248, 1932.

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31. Olef, I.: The Rate of Disintegration of Platelets, J. Lab. & Clin. Med. **22**:128, 1936. König.[4]

32. Rosenthal, N.: Clinical and Hematological Studies on Banti's Disease, J. A. M. A. **84**:1887 (June 20) 1925.

33. Patey, P. H., in Discussion on Postoperative Thrombosis, Proc. Roy. Soc. Med. **22**:733, 1929.

34. (*a*) Bryce, A. G.: Splenectomy and Thrombosis, Lancet **2**:1423, 1932. (*b*) Mackay, W.: The Blood Platelet: Its Clinical Significance, Quart. J. Med. **24**: 285, 1924. (*c*) Evans and Fowler.[6]

35. Olef, I.: The Differential Platelet Count: Its Clinical Significance, Arch. Int. Med. **57**:1136 (June) 1936.

large pulmonary embolism. Autopsy revealed the presence of large antemortem clots in the periprostatic veins and the inferior vena cava.

In this person two phenomena were observed: a high thrombocyte count and a postoperative thromboembolic accident. Suggestive as they are, however, they offer none but the usual suppositious evidence for the platelet factor in thrombosis. In the first place, the increase in the platelets was not actually postoperative, since the count of 1,221,000 per cubic millimeter was made three days before operation. Furthermore, there were present in this series of studies 4 other platelet levels above 1,000,000 per cubic millimeter, 1 occurring in a preoperative patient with a bleeding gastric ulcer, another occurring on the twenty-first day following cecostomy (chart 1) and the remaining 2 occurring in the 2 splenectomized patients. None of these patients exhibited any clinical evidence of thrombosis or embolism.

CONCLUSIONS

1. A substantial postoperative rise in the level of the blood platelets is a phenomenon which occurs commonly, though not without exception.

2. The degree and time of the maximal elevation are variable, although a majority of the patients show the maximal rise between the tenth and the fifteenth postoperative day.

3. No definite correlation between the extent of the operation and the degree of the postoperative rise can be established, although a rough relationship is suggested.

Dr. John S. Lawrence gave encouragement and advice throughout this work.

ELECTRIC SHOCK THERAPY IN A GENERAL HOSPITAL

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DETROIT

There has been sustained interest in the shock therapies since 1932, when Sakel [1] introduced insulin coma for schizophrenia. Its use for several years was rather empiric, and today it is used only in selected cases. In 1935 Meduna [2] added metrazol convulsive therapy to the treatment of schizophrenia. It was soon found, however, to be most effective for the depressed states, particularly the reactive depressions. It was heralded as a specific for the depressions but was frowned on because of its orthopedic complications and the fears patients expressed toward it.

It is five years since electric shock therapy was introduced by Cerletti and Bini.[3] There are now available a sufficient number of reports on this therapy to permit some definite conclusions. Electric shock has been accepted with considerable enthusiasm; and, although most investigators have been disappointed by their results in the treatment of some psychoses, particularly schizophrenia, it is an almost specific therapy for the depressions.

The purpose of this paper is to review the present status of electric shock therapy and to present an additional 100 cases. We feel that these cases will be of particular interest because most of them deal with mental disease in its incipiency, many of the patients having been referred from the offices of general practitioners or of specialists who recognized in their patients the need for psychiatric care. Included, too, are the cases of treated patients who had been under our care for some time in our hospital or our outpatient clinic.

Electric shock therapy has almost completely replaced metrazol convulsive therapy because of certain advantages in its administration, most obvious of which is the absence of apprehension or panic in the patient, which was commonly encountered with metrazol. In addition to this, the seizure with the electric shock method can be more uniformly produced in a given person than it can with the drug method. Also, the seizure with electric shock is not so severe, and its resulting complications, therefore, are not so frequent.

The apparatus used in electric shock is a compact unit and easily carried. There are several makes available, but all are built on the same plan. Ordinary alternating "house" current of 80 to 150 volts is used, and the strength is set in milliamperes varying from 300 to 650 and flowing for one tenth to eight tenths of a second. We have used 110 volts with the milliamperage between 400 and 450 for three tenths or five tenths of a second in the average case. We produced the desired response in 1 patient with 350 milliamperes for three tenths of a second, and 1 patient required 650 milliamperes for five tenths of a second to produce a convulsive response. Generally speaking, the strength of the current required depends on the size of the patient—the larger the subject the greater the strength required. This is, however, by no means the rule.

There are three types of reaction which may occur. Smith, Hughes and Hastings [4] called these the "missed," the "equivalent" and the "grand mal" reaction. In the missed reaction there is a sudden start with almost immediate consciousness and no recollection of the episode. In the equivalent reaction there is the sudden start but the patient does not regain consciousness for a period of seconds to minutes. There is usually apnea during this period. There may be some spasticity and twitching of the extremities. The patient then rouses slowly during the next ten to fifteen minutes. Some believe this reaction to be equivalent therapeutically to the convulsive, or grand mal, response. We do not believe this to be the case, and we endeavor to produce the grand mal reaction. In the last type, again, is the same start and the patient may im-

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1. Sakel, M.: Neue Behandlungsmethode der Schizophrenia, Vienna, Moritz Press, 1935.

2. Meduna, L.: New Methods of Medical Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **35**:361 (Feb.) 1936.

3. Cerletti, U., and Bini, L.: Un nuovo metodo di shockterapia: "l'elettro-shock" (riassunto), Boll. ed. atti d. r. Acad. med. di Roma **64**:136, 1938.

4. Smith, L. H.; Hughes, J., and Hastings, D. W.: First Impressions of Electroshock Treatment, Pennsylvania M. J. **44**:452, 1941.

mediately go into a generalized epileptiform seizure or there may be a short latent period before the seizure. The seizure lasts between fifteen and sixty seconds. Following this, there is usually a period of apnea, and then the patient begins breathing loudly and moistly. There may be a period of excitement and then confusion for fifteen to thirty minutes.

Prior to giving a patient electric shock therapy it has been our rule to have the family sign a permit, explaining the complications and the dangers associated with the treatment. After this is done, in addition to the routine physical and neurologic examinations and studies of the blood and urine, we make an electrocardiographic tracing and a roentgenogram of the thoracic portion of the spine, anterior and posterior. Electric shock therapy should not be used in the presence of coronary disease or advanced heart disease. The roentgenogram of the spine is to rule out pathologic conditions of the bones. Compression fractures which may occur almost always involve the thoracic area. We avoid sedation as much as possible for twelve hours before treatment. The patient should have no food for two hours before treatment, and artificial dentures and bridgework should be removed.

The contraindications for convulsive therapy, in addition to advanced heart disease and pathologic conditions of the bones, are organic disease of the brain, advanced arteriosclerosis, active tuberculosis and thrombophlebitis. Naturally, there are times when therapy may be indicated even in the presence of one or more of these conditions. Jones and Pleasants[5] have used electric shock for highly agitated patients with dementia paralytica prior to giving them hyperpyrexia. Evans[6] reported the case of a woman with generalized osteoporosis to whom he gave metrazol convulsive therapy. Evans[7] also reported giving electric shock therapy to a 74 year old woman with a complete left bundle branch block without untoward complications.

The number of treatments given varies with the individual case. We have given as few as one treatment and as many as twenty-four. Kay, Smith and Reim[8] reported that they gave 1 patient sixty-one treatments, and we believe this to be a record high. The average course of treatment for a depression is eight; a manic-depressive psychosis requires about twelve, schizophrenia at least ten and a psychoneurosis between two and six. The treatments are usually given two or three times each week. We have found that this is not frequent enough for the extremely agitated patients with depression or for the highly active manic patients. Therefore, certain patients are given daily treatments for four or five consecutive days and then every other day as indicated by their response or by the nature of their condition.

The most common serious complication in electric shock therapy is compression fracture of the thoracic portion of the spine. As has been mentioned, roentgenograms of the thoracic portion of the spine are taken before therapy to rule out the presence of pathologic changes in the bones which might predispose the patient to this complication. We have used curare routinely for our patients receiving electric shock, and we feel that chances for fracture are greatly reduced. It is rather impracticable to make a roentgenogram after each treatment. However, if the patient complains of any pain referable to the thoracic portion of the spine after a treatment, a roentgenogram is made before another treatment is given. It is of interest to note that Smith, Hughes, and Hastings,[4] who reported a series of 80 cases, had found four compression fractures which were asymptomatic and discovered on routine roentgen examination at the completion of the course of treatment. Another complication is dislocation, particularly of the shoulders and of the lower jaw. Defect of memory after treatment is fairly common, but it is a change into which the patient has insight. It is not a serious complication, and in our experience it always disappears. Muscular soreness may occur after the more severe convulsions. Headache is not uncommon, but it is rarely serious and it can be controlled with average doses of the ordinary analgesics. Nausea occasionally occurs, but vomiting is rare.

Restraint and postural measures are of value in preventing "jack-knifing," which supposedly causes compression fractures. It seems probable that "jack-knifing" is not the whole answer to compression fracture. The development of the skeletal musculature must play a large part in producing these compression fractures. Hence, postural precautions alone cannot be depended on to prevent this complication. Curare, which was first used by Bennett[9] in metrazol therapy,

5. Jones, G. L., and Pleasants, E. N.: Curare Modification of Therapeutic Convulsions, Dis. Nerv. Syst. **4**:17 (Jan.) 1943.

6. Evans, V.: Metrazol Shock Therapy in Presence of Generalized Osteoporosis: Report of a Case, Arch. Neurol. & Psychiat. **46**:535 (Sept.) 1941.

7. Evans, V.: Convulsive Shock Therapy in Elderly Patients: Risks and Results, Am. J. Psychiat. **99**:531 (Jan.) 1943.

8. Kay, F. A.; Smith, J. D., and Reim, N. H.: Electroshock Treatment in Psychiatric Disorders, J. M. A. Alabama **12**:129 (Nov.) 1942.

9. Bennett, A. E.: Curare: A Preventive of Traumatic Complications in Convulsive Shock Therapy, Am. J. Psychiat. **97**:1040 (March) 1941.

comes near to eliminating compression fractures completely. Curare acts on the myoneural junction, probably by neutralizing acetylcholine, and thus prevents the response of striated muscle to the nerve impulse. For some reason, the intercostal muscles and the diaphragm are more resistive to the drug than the ordinary skeletal muscles. Therefore, one can calculate a dose that will soften the convulsion but will not interfere with respiration.

Most therapeutists have used curare only for those of their patients who seemed most susceptible to fracture. We have used it routinely and in smaller doses than those used by Bennett for metrazol therapy. Also, rather than use weight alone as an index for the dosage of curare, we have taken into consideration the general muscular development of the patient. We have found that 2 cc. of curare given intravenously is the "working dose." This is the dose that will give satisfactory curarization of an adult weighing 140 pounds (63.5 Kg.) and of average musculature. We have given between 1.5 and 3.5 cc. One minute is taken to inject the drug, and the treatment is given two minutes after the injection is completed.

The first 100 cases in which we have used the electric shock treatment cover a period of eleven months; hence the duration of the follow-up study varies between one and ten months. For the purpose of simplifying our statistics we have indexed the diseases of our patients as: (1) depressions, (2) schizophrenia, (3) manic-depressive psychoses and (4) psychoneuroses. Obviously, there may be some overlapping. Included in the depressions are involutional melancholia, reactive depressions and depressions with mixed components, including menopausal symptoms. We have been interested especially in the immediate results obtained with electric shock. Even the most pessimistic observer must agree that it alters the psyche within a short time and makes possible a psychotherapeutic approach that may not have been possible before the treatment. The results in treatment of the reactive depressions, involutional melancholias and endogenous depressions, as classified by Fetterman,[10] are often dramatic. Two cases in point are briefly described:

CASE 1.—C. B., a married man of 50, was admitted to the hospital on Dec. 31, 1942, with a history of having been extremely nervous for three months. In the three weeks preceding his admission he had become depressed and had mentioned suicide on several occasions. He had made vague statements of having embezzled funds from the city, for which he had worked some years in a responsible position.

A more detailed history, obtained from members of the patient's family, disclosed that the patient had held a nonpolitical job with the city for over twenty years. More recently the job had come under political influence, and apparently there had been some pressure to replace him. It finally became necessary for the patient to undergo competitive examinations to continue in his position. He passed these examinations with higher grades than his competitors, but he felt unable to accept his former responsibilities and resigned.

On admission to the hospital he was confused, agitated and suicidal. He was deeply depressed. Physical examination revealed nothing unusual except for evidence of vitamin C deficiency. He was treated symptomatically for twenty-five days and showed little improvement. On January 26 he was given his first electric shock treatment, and a grand mal reaction was obtained. He showed considerable improvement after this first treatment, and he was given two additional treatments, on January 28 and 29. After these he appeared completely changed. He took interest in his surroundings and began associating with fellow patients. His family stated that he was "his old self." He was discharged from the hospital on February 3. He has been followed in the outpatient clinic and has continued well. It was arranged that he return to work in a new position on June 1, 1943.

CASE 2.—M. M., a married woman of 45, was admitted to the hospital as a psychiatric patient on Dec. 2, 1942. She was transferred to our care from one of the state hospitals for the insane, where she had been a patient for twelve months. Born in Scotland, she had come to the United States at 25 years of age and had married a short time later. At 31 years she gave birth to a son. Her marital life had been normal, and apparently she had always been a stable person until two months prior to her commitment to the state hospital. At that time she began quarreling over trivial matters with some of her relatives by marriage. After an argument with her sister-in-law she told her husband that she herself had been wrong and that God would punish her. She began to have many persecutory ideas and became highly agitated. She ate little and lost considerable weight. An attending physician advised hospitalization. Because of limited funds she was committed to the state hospital. During her twelve months in the state hospital she showed a change in her menstrual cycle and was treated symptomatically. She did not respond to such treatment. She continued to have persecutory ideas. Because the financial status of the husband had improved with the advent of defense work, he asked that his wife be transferred to our hospital for further treatment so that she could be nearer home.

Twelve days after her admission, on Dec. 14, 1942, the patient was given her first electric shock. After her third treatment she became rational, asked about her illness and seemed normal. She wrote her sister in Scotland the first letter she had written in over a year. Two days later she had a relapse and the shock treatment was continued. In all she was given eleven treatments, eight of which produced grand mal reactions and three of which produced equivalent reactions. Her improvement was dramatic, and, although further hospitalization was advised, the husband asked that his wife be given a trial at home. We consented to his request. On February 3 she was discharged from the hospital to the outpatient service. She had gained 13 pounds (5.9 Kg.). She has continued to do well at home and has accepted the responsibility of her home.

10. Fetterman, J. L.: Electro-Coma Therapy of Psychoses, Ann. Int. Med. **17**:775 (Nov.) 1942.

Of the 100 patients treated, 32 have had schizophrenia; 31, depressions; 25, psychoneuroses, and 12, manic-depressive psychoses.

In recording our results we have placed the patients in three categories which we shall refer to as improved, less improved and least improved. In the improved group we have placed the patients who have improved to the extent that they are able to return to their former responsibilities. In the less improved group we have placed the patients who have improved but not to the extent that they are able to accept all of their former responsibilities. In the least improved category we have placed the patients who do not fit into either of the first two groups. Many of those placed in the least improved category had actually improved as compared with their condition on admission, but, nevertheless, they were unable to accept any responsibilities and had to be under further care either in an institution or at home.

The table graphically records our results.

Results of Treatment

Illness Treated	Number of Patients	Improved	Less Improved	Total	Least Improved
Schizophrenia.....	32	9 (28.1%)	15	24 (75%)	8
Depression.....	31	24 (77.4%)	3	27 (87%)	4
Psychoneurosis....	25	6 (24%)	16	22 (88%)	3
Manic-depressive psychoses.....	12	5 (41.7%)	2	7 (58.4%)	5

It is of interest to note that in the improved group there are only 9 of the 32 persons with schizophrenia treated, or 28.1 per cent. However, if the improved and the less improved group are combined, there are 24 of 32 treated, or 75 per cent. Of the patients with depression, there are 24 of 31 in the improved group, or 77.4 per cent. The percentage increases to 87 when the improved and the less improved group are combined. Of the 25 patients with psychoneuroses treated, only 6, or 24 per cent, can be placed in the improved group, while this figure rockets to 88 per cent for the combined group. Of the 12 patients with manic-depressive psychoses treated, 5, or 41.7 per cent, are in the improved group and 58.2 per cent in the combined category.

There is some question as to the usefulness of electric shock in treatment of the manic-depressive psychoses, and with only 12 patients in our series our data are insufficient for any conclusion. Reed [11] expressed the opinion that the therapy is of value in that it reduces the period of illness to a few weeks and encourages the patient to return immediately for treatment when the next attack occurs. Myerson [12] made the point that it does not seem advisable to give electric shock in cases in which the manic-depressive cycle repeats itself every few months or more often. Our impression is that electric shock is a valuable aid in the management of the highly manic or noticeably agitated depressed phase of this psychosis, but the treatment does not have the specificity that it has for the reactive depressions.

It is generally conceded that electric shock therapy is of doubtful value in the treatment of schizophrenia. This deduction receives support from our results when it is noted that only 28.1 per cent of the treated patients with schizophrenia can be placed in the improved group. However, the 75 per cent in the combined group suggests that the schizophrenic patient may be aided somewhat, often to the extent that he can be managed more easily by his family and can even accept some light responsibility.

Electric shock treatment of psychoneurotic patients has been discouraging in our experience. Our percentage in the improved category is low. It seems that psychotherapy is of greatest value in the treatment of the psychoneuroses and the only value of electric shock is to facilitate a better approach in a psychotherapeutic way.

Electric shock is an almost specific therapy for the depressions, as is reflected in the high percentage of (77.4 per cent) patients in the improved category and in the combined group (87 per cent).

In the comparatively short follow-up period relapses in our patients have not been frequent. Some with depressions who had a relapse responded well to a second and shorter course of treatment. Some of these relapses have been mild enough for the patients to continue with the treatment in the outpatient department.

Our complications in electric shock with the routine use of curare have been almost negligible. We have had 2 compression fractures of the thoracic portion of the spine. One of the fractures occurred in a large and muscular man who apparently was not sufficiently curarized by the prescribed dose. The other fracture was also in a male who had three treatments accompanied by the use of curare. As he was being prepared for his fourth treatment, he objected to the intravenous injection of curare, and, rather than force him to take the injection, we administered the treatment without the curare. Shortly after awakening from the treatment the patient began

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12. Myerson, A.: Further Experience with Electric-Shock Therapy in Mental Disease, New England J. Med. **227**:403 (Sept. 10) 1942.

to complain of tenderness and soreness in the upper thoracic portion of his spine. A roentgenogram was taken, which showed a compression fracture of the fifth thoracic vertebra. Neither of these 2 patients had any untoward complications, and neither was placed in a body cast.

There were no dislocations or other fractures in our series, nor were there any other serious complications. For 1 patient we discontinued treatment because in both treatments given there occurred a cardiac arrest.

SUMMARY AND CONCLUSIONS

General hospitals with neuropsychiatric facilities can utilize electric shock therapy to advantage. In a general hospital of six hundred beds 100 patients were successfully treated over a period of eleven months.

Electric shock therapy has largely replaced metrazol convulsive therapy. It appears to be almost a specific therapy in the treatment of the depressions whether they are endogenous, involutional or reactive or depressions with mixed components. The therapy is not of great value for schizophrenia, although it does seem to make many of the patients more manageable. Its use for the manic-depressive psychoses is primarily to facilitate management. The use of this therapy for frequent recurrences of this psychosis is questionable. For the psychoneuroses the results are rather discouraging, probably because the underlying determinant must be removed to relieve the psychoneurotic state properly; electric shock is judged to be of some benefit in facilitating the psychotherapeutic approach.

Curare was used routinely in the treatment of our 100 patients. The only serious complication was compression fracture of the thoracic portion of the spine. This occurred in only 2 cases, and in 1 of these the fracture occurred when the curare was unwittingly omitted after it had been used in earlier administrations.

USE OF A SYNTHETIC DIET FOR FOOD ALLERGY AND TYPHOID

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An attempt has been made to construct a diet for man as nearly as possible free of natural foods and composed of nutritional factors in chemically pure form. The need for such a diet may occur in three conditions. First, since a mixture of amino acids is not antigenic, one may support normal nutrition for persons with severe food allergy and at the same time determine whether food plays an important role in the manifestations of allergy exhibited by the patient. When the patient is allergic to food, the feeding of such a diet should result in definite improvement. Secondly, mixtures of amino acids and dextrose, since they are both crystalline, are rapidly absorbed in the upper portion of the intestinal tract. Pure fats may be emulsified so that they can be absorbed as rapidly as natural ones. Thus, when there is ulceration of the lower part of the intestinal tract one might expect such a diet to be more rapidly and easily absorbed than natural foods composed of proteins and starches. Thirdly, as when purified diets are fed to animals it may be possible to determine accurately the requirement for a single vitamin, both under normal circumstances and in pathologic conditions in which it is suspected that requirements are increased. The purpose of this paper is to record our experience in the use of a synthetic diet under two of these conditions: first, when given to patients with various types of allergy in whose cases there was some question whether food was an important factor and, secondly, to patients who were suffering from typhoid.

NUTRIENTS AVAILABLE FOR MAKING A SYNTHETIC DIET

In 1935 Rose [1] discovered the last of the amino acids, threonine. This amino acid added to those already known made it possible to place rats on a nonprotein diet on which they could grow normally and reproduce. In 1940 Mueller, Kemmerer, Cox and Barnes [2] produced an enzymatic digest of casein which would support the growth of experimental animals. This digest contains 12.5 per cent of nitrogen, of which 7.4 per cent is amino acids, the remainder presumably being composed of polypeptides. Guinea pigs could not be sensitized to the amino acid mixtures. Other workers [3] have shown that infants can be kept in nitrogen balance during both oral and parenteral administration of amino acid mixtures. McGee and Emery [4] studied the rate of absorption of the amino acid mixture from the small intestine of man by means of the Miller-Abbott tube. They showed that the amino acid mixture is absorbed twice as fast as casein or gelatin. Elman and his associates [5] have used the amino acid mixtures intravenously and have been able to support the metabolism of various patients who could not take food by mouth. They were able to keep patients in nitrogen equilibrium, and they have been able to give as much as 300 Gm. intravenously in twenty-four hours without serious reactions.

Dextrose is obviously the best source for carbohydrate in such a food mixture. Its rate of absorption was studied by Cori [6] in animals

From the Department of Internal Medicine, Washington University School of Medicine.

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4. McGee, L. C., and Emery, E. S.: Rate of Absorption of Amino Acids from the Small Intestine in Man, Proc. Soc. Exper. Biol. & Med. **45**:475, 1940. Zetzel, L.; Banks, B. M., and Sagall, E.: Intestinal Absorption of an Amino-Acid Mixture in Patients with Chronic Idiopathic Ulcerative Colitis and Enterocolitis, Am. J. Digest. Dis. **9**:350, 1942.

5. Elman, R., and Weiner, D. O.: Intravenous Alimentation with Special Reference to Protein (Amino Acid) Metabolism, J. A. M. A. **112**:796 (March 4) 1939. Elman, R.: Protein Deficiency in Surgical Patients and Its Correction, J. Am. Dietet. A. **18**: 141, 1942; Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein, Ann. Surg. **112**:594, 1940.

(Footnotes continued on next page)

and later by Groen [6] in man by means of the Miller-Abbott tube. The latter observer confirmed Cori's results for animals, showing that dextrose is rapidly absorbed from the first part of the small intestine. It is absorbed at such a rapid rate that the question of flooding the blood with it has to be considered. To avoid too rapid absorption the feeding tube is admirably suited, since smaller feedings can be given hourly or at two hour intervals continually throughout the twenty-four hours.

The fat in a mixture of purified food materials presents a more difficult problem than that of the nitrogen or the carbohydrate. Glycerides of pure fatty acids have not been available to us, but the oils of corn, olive and hydrogenated cottonseed are available and not expensive. Tottingham [7] has given the analysis of these oils and stated that in corn oil and cottonseed oil there are about 40 per cent of linoleic acid and small amounts of arachidonic acid. Since it has been shown that linoleic and arachidonic acids are acids which animals cannot synthesize, one has in these oils an abundant source of the essential fatty acids. There is no way of accelerating the absorption of fatty acids from the intestinal tract, because bile and lipase are necessary for that operation; but emulsification is the initial step in the process of absorption, and it can be easily accomplished when one is making up the feeding mixture.

In using a mixture of amino acids, dextrose and corn or cottonseed oil as a source for the purified nutrients, one must add the inorganic nutrients in the form of a salt mixture. The amino acids cystine and methionine contain sulfur, and in the amounts of the amino acid mixture that we use there would be about 600 mg. available in twenty-four hours. Requirements for the human adult are probably in the region of from 600 to 1,000 mg.[8] The other inorganic elements that are essential to human nutrition are calcium, phosphorus, magnesium, sodium, potassium, chlorine, iron, copper, zinc, manganese, iodine, fluorine and cobalt. In the ordinary diet all these inorganic elements occur in sufficient amounts in natural foods, except, of course, sodium and chlorine. Most of the requirements of these elements are fairly well known, so that a salt mixture for human requirements can be put together without much difficulty. We have tried Cowgill's [9] salt mixture which he has fed to dogs but have found that it exerts a cathartic action when given to man. Table 1 gives the mixture of salts we have used,

TABLE 1.—*Salt Mixture (Twenty-Four Hour Requirement)*

	Gm.		Gm.
Calcium phosphate	1.75	Potassium chloride	1.60
Calcium carbonate	0.80	Sodium acid phosphate	2.50
Potassium acid phosphate	2.50	Sodium chloride	5.50
Potassium acid carbonate	4.00	Manganese carbonate	1.00
Trace Elements			
	Mg.		**Mg.**
Ferrous sulfate	100	Copper sulfate	2.5
Potassium iodide	0.065	Zinc sulfate	2.5
Manganous sulfate	0.30		

and table 2 shows the daily supply of elements that this mixture supplies. The mixture has been used for a number of persons, both normal and sick, and found to be noncathartic.

The following vitamins are available in purified form: carotene (provitamin A), activated ergosterol, menadione (2-methyl-1, 4-naphthoquinone), thiamine, riboflavin, nicotinamide, pyridoxine, calcium pantothenate, ascorbic acid and choline chloride. Some of these ten vitamins are known to be required by the human being, while others may be needed under stress of a severe infection. It has been shown that biotin is needed only when excessive amounts of egg white have been fed to human beings,[10] just as it is required by experimental animals. Inositol is an alcohol widely present in muscle and many tissues and has been shown to be a vitamin essential for the mouse.[11] Whether the

TABLE 2.—*Elements Supplied by 19.655 Gm. of Salt Mixture (Twenty-Four Hour Requirement)*

	Gm.		Mg.
Calcium	1.00	Iron	20
Phosphorus	1.48	Iodine	0.06
Potassium	3.06	Manganese	0.10
Sodium	2.58	Copper	1.0
Chlorine	4.00	Zinc	1.0
Magnesium	0.29		

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7. Tottingham, W. E.: Plant Biochemistry, Minneapolis, Burgess Publishing Company, 1937, pp. 66.

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9. Cowgill, G. R.: An Improved Procedure, for Metabolism Experiments, J. Biol. Chem. **56**:725, 1923.

10. Sydenstricker, V. P.; Singal, S. A.; Briggs, A. P.; De Vaughn, N. M., and Isbell, H.: "Egg White Injury" in Man and Its Cure with a Biotin Concentrate, J. A. M. A. **118**:1199 (April 4) 1942.

11. Woolley, D. W.: A New Dietary Essential for the Mouse, J. Biol. Chem. **136**:113, 1940.

human being can synthesize it is not known. Vitamin E has not been shown to be essential for the human being.[12] Probably the most essential of the vitamins have been discovered, but undoubtedly there are others which man may need to a lesser degree than those that are now known. One can safely give a synthetic diet to which these ten vitamins have been added for a period of two weeks, especially at a time when the metabolism of the patient is normal. However, if there is infection or elevation of metabolism it is probably necessary to add a liver concentrate, so that other vitamins now unknown will be present in the food mixture. The liver extract that we have employed has been widely used in this manner for animals. Choline is added to the diet because it has been shown in experimental animals that larger amounts of choline than can be synthesized[13] are needed by the fast-growing animal; and, since the metabolism in fever is greatly elevated, it is well that there should be a ready supply of the methyl groups from choline.

TABLE 3.—*Caloric Value of Synthetic Diet*

Calories	24 Hr. Volume, Cc.	Amino Acids,* Gm.	Fat, Gm.	Dextrose, Gm.	Salt Mixture, Gm.
1,500	1,080	42	84	150	16
2,000	1,440	56	112	200	16
2,500	1,800	70	140	250	20
3,000	2,160	84	168	300	24
3,500	2,620	98	196	350	28
4,000	2,880	112	222	400	32

* Amigen, furnished by Mead Johnson & Co., Evansville, Ind.

PREPARATION OF THE DIET

A master diet of 2,500 calories containing 70 Gm. of amino acids, 140 Gm. of oil, 250 Gm. of dextrose and 20 Gm. of the salt mixture is made up to a volume of 1,800 cc. By feeding less or more of this standard mixture the calories can be varied from 1,500 to 4,000, as table 3 shows. This standard technic makes the work of the dietitian simple; however, a mixture of amino acids, fat and dextrose may be made up in almost any volume desired.

The dextrose, amino acids and salt mixture are dissolved in 1,000 cc. of tap water by the use of a mechanical mixture. Eight grams of powdered pure gelatin is dissolved in 75 cc. of warm tap water and allowed to stand twenty minutes so that the gelatin will be completely dissolved; then the gelatin solution is beaten in a mechanical mixer or with a Dover beater and the oil is added, in the beginning in small quantities. When all the oil is emulsified, it is diluted with the solution of dextrose, amino acids and salts and the total volume made up to the desired quantity with water. We have found that corn oil and cottonseed oil are emulsified easily and remain in emulsion well; this is not so true of olive oil. Undoubtedly the salts aid materially in the emulsification and the stability of the emulsion. Since gelatin is a substance to which few persons are allergic, it is our material of choice as an emulsifier. Agar is better in many respects, but we have found it too cathartic. The other hemicelluloses that have been tried have not been satisfactory.

The vitamins are given by the nurse in charge of the patient. Table 4 shows the doses of vitamin and vitamin materials used under the two conditions we are discussing. Thiamine, riboflavin, nicotinamide, pyridoxine and calcium pantothenate were given in the form of a tablet. This tablet contained 5 mg. of thiamine and riboflavin, 25 mg. of nicotinamide and calcium pantothenate and 10 mg. of pyridoxine. For convenience it is referred to as T R N 6 P. It will be noted that the daily dose of the five crystalline members of the B complex is large. We believe these amounts desirable because in many instances food allergy results in voluntary restriction of the vitamin-rich foods. Table 5 gives the schedule of vitamin supplements as administered both to patients with typhoid and to allergic persons.

TABLE 4.—*Dosage of Vitamins*

For Normal or Allergic Persons	
Vitamin A (carotene)	10,000 U.S.P. units
Vitamin D (activated ergosterol)	500 U.S.P. units
*Thiamine	5 mg.
Riboflavin	5 mg.
Nicotinamide	25 mg.
Pyridoxine	10 mg.
Calcium pantothenate	25 mg.
For Patients with Typhoid	
Vitamin A (halibut liver oil)	60,000 U.S.P. units
Vitamin A (halibut liver oil)	5,000 U.S.P. units
*Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Nicotinamide	50 mg.
Pyridoxine	20 mg.
Calcium pantothenate	50 mg.
Ascorbic acid	200 mg.
Choline chloride	1 Gm.
2-methyl-1,4-naphthoquinone (menadione)	2 mg.
†Liver powder	20 Gm.

* Thiamine hydrochloride, riboflavin, nicotinamide, pyridoxine and calcium pantothenate furnished by Merck & Co., Inc., Rahway, N. J.

† Liver powder furnished by Wilson & Co., Inc., Chicago. Dr. David Klein informed us that this powder contains per gram: 10 U.S.P. units of vitamin B_1, 325 micrograms of riboflavin, 500 micrograms of pantothenic acid, 40 micrograms pyridoxine and 1.5 milligrams of nicotinic acid. In addition, it contains choline and a large number of other factors not as yet precisely defined.

The taste of this mixture is not pleasant. Though some persons were found who did not mind taking it by mouth, most persons find it offensive. For this reason a no. 12 Levin tube was inserted into the stomach and left in place during the course of the feedings. Feedings were given at intervals of two to four hours.

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USE OF SYNTHETIC FEEDING IN ALLERGY

As a cause for the manifestations of allergy, food is often an important factor, especially when these manifestations involve the skin or the intestinal tract.[14] The diets suggested by Rowe [15] for the elimination of most of the troublesome foods are without doubt useful; but if any criticism can be made it is that they are not usually adequate in calories, calcium or vitamins A and C, and care is necessary to prevent malnutrition. Also, the physician never knows whether the patient may not be one of the rare persons who are sensitive to one or more of the foods which make up the Rowe diets. When the physician wishes a diet to fulfil two requisites, namely, one that is adequate in calories, minerals and the important vitamins and at the same time furnishes nitrogen free from protein (except for a small amount of gelatin), a synthetic diet such as suggested will be found most useful. The following brief case histories illustrate the types of patients to whom the diet has been given, and table 6 summarizes the data.

TABLE 5.—*Schedule of Vitamin Supplements for Patients with Typhoid*

Time of Feeding	Vitamins to Be Added
7 a. m.	1. 5 drops halibut liver oil 2. 1 mg. 2-methyl-1,4-naphthoquinone (menadione) 3. 1 teaspoon choline chloride solution (1 Gm.) 4. 1 tablet T R N 6 P crushed
9 a. m.	1. 5 drops halibut liver oil 2. 1 ascorbic acid tablet crushed
11 a. m.	1. 5 drops halibut liver oil 2. 1 ascorbic acid tablet crushed
1 p. m.	1. 5 drops halibut liver oil 2. 1 teaspoon choline chloride solution (1 Gm.) 3. 20 Gm. of liver powder
3 p. m.	1. 5 drops halibut liver oil 2. 1 ascorbic acid tablet crushed
5 p. m.	1. 5 drops halibut liver oil 2. 1 ascorbic acid tablet crushed
7 p. m.	1. 5 drops halibut liver oil 2. 1 mg. 2-methyl-1,4-naphthoquinone 3. 1 teaspoon of choline chloride solution (1 Gm.) 4. 1 tablet T R N 6 P crushed
9 p. m. 11 p. m. 1 a. m. 3 a. m. 5 a. m.	To each of these feedings 5 drops of halibut liver oil is added.

CASE 1.—A 15 year old girl entered the hospital because of a dermatitis of fourteen years' duration. The dermatitis covered the wrists, backs of the hands, popliteal spaces and ankles. The skin was rough, with reddened areas and many scratch marks, and was covered with hemorrhagic crusts. About two years previously the patient had had two attacks of asthma. There was also a history of vomiting after eating spinach or eggs. The dermatitis was improved in the summer or when she was exposed to ultraviolet radiation.

Tube feedings were continued for twenty-three days, and no improvement was noticeable. Later treatment with human dander extract and hemolytic Staphylococcus aureus vaccine produced definite improvement.

CASE 2.—A woman of 38 entered the hospital because of eczema of the face, neck, ears and axillas and to a less extent the whole body. Her skin was thickened, dry and reddened and in places covered with bloody crusts. Tube feedings were carried out for five days; immediate improvement was striking.

CASE 3.—A woman of 51 entered the hospital because of purpura. A fine purpuric rash was distributed over the whole body. She was able to take the feedings by mouth, and they were continued for eleven days. The purpura faded rapidly and had entirely disappeared by the end of a few days. There was a reappearance of the purpura following the use of carmine capsules, but again the purpura disappeared rapidly. The final decision was that the purpura was probably of food origin, the relapse being due to the dye.

CASE 4.—A woman aged 20 entered the hospital with bronchial asthma. The asthma was thought to be intrinsic. It had been present since the age of 8 years. There was a definite bacterial infection of the sinuses. The diet was given for five days, and there was some improvement during that time. She was able to do without epinephrine, although its use had been constant.

This case illustrates the fact that even in bronchial asthma, food may be of minor but of some importance from a therapeutic viewpoint.

TABLE 6.—*Data for Allergic Patients Given Synthetic Diet*

Diagnosis, Sex and Age (Yr.)	No. of Days Diet Taken	Method of Administration	Progress While on Diet	Foods as an Etiologic Factor
Neurodermatitis..... ♀ 15	23	Tube	No improvement	None
Eczema..... ♀ 38	5	Tube	Improvement rapid	Important
Purpura..... ♀ 51	11	Mouth	Improvement rapid	Important
Bronchial asthma... ♀ 20	5	Mouth	Improvement	Minor but definite
Colitis (allergic)..... ♀ 48	2	Tube	Complete relief	Complete
Neurodermatitis..... ♀ 36	12	Tube	Improvement	Important
Henoch's purpura... ♀ 15	14	Tube	Great improvement	Important
Colitis; purpura..... ♀ 35	3	Tube	Complete relief	Complete
Purpura (abdominal pain)..... ♀ 20	14	Tube	Partial relief	Minor or none

CASE 5.—A woman of 48 came into the hospital because of spells of diarrhea which had been present for six to seven years, and at the time of admission the diarrhea had been constant. The barium sulfate enema showed the colon to be extremely irritable, with deep irregular haustra. Tube feedings were carried out for only two days, but as soon as the mixture was given the diarrhea stopped immediately. Observations following the tube feedings showed that the patient was allergic to corn, celery, peas, cabbage, milk, beans, bran and coconut.

14. Hampton, S. F.: Henoch's Purpura Based on Food Allergy, J. Allergy **12**:579, 1941.

15. Rowe, A. H.: Elimination Diets and the Patient's Allergies, Philadelphia, Lea & Febiger, 1941.

CASE 6.—A Negro woman of 36 entered the hospital because of neurodermatitis. The lesion involved the elbows and the popliteal spaces. A great deal of lichenification was present. The eosinophil count was 16 per cent. Tube feedings were continued for twelve days. The improvement was slow but steady, and it was thought that the case illustrated the type of neurodermatitis responding to the elimination of foods to which the patient was sensitive.

CASE 7.—A child 15 years old entered the hospital because of Henoch's purpura. Tube feedings were given for fourteen days. The abdominal pain ceased abruptly; the purpura of the skin cleared, and the symptoms of colitis improved rapidly. It was found that the patient was sensitive to milk. She was discharged from the hospital, but after a period of complete freedom from symptoms she again ingested large amounts of milk. This was followed by a return of her symptoms, and when she entered the hospital for the second time she was extremely ill, showing severe ascites, a great reduction in the plasma albumin, an enlarged spleen and an intense bloody diarrhea. Again the patient was given tube feedings, and large amounts of vitamins were administered—15 mg. daily of thiamine and riboflavin, 75 mg. of nicotinamide, 30 mg. of pyridoxine and 75 mg. of pantothenic acid. In addition, the liver concentrate was given. Protoscopic examination showed at the beginning pronounced edema with petechial hemorrhages of the mucosa but no ulceration. At the end of her treatment the mucous membrane was entirely normal; the proctoscope was introduced 20 cm. and it was noted that the colon was extremely irritable to touch, the slightest injury causing some bleeding. The roentgen diagnosis was typical ulcerative colitis.

The case illustrates the secondary effects of long-continued allergic colitis. The roentgen picture, typical of ulcerative colitis, was apparently due to the edema of the walls of the colon.

CASE 8.—A white woman of 35 entered the hospital because she was anxious and upset as to what she should eat. She had lost 20 pounds (9.1 Kg.) in weight and showed purpuric hemorrhages over the skin. She complained bitterly of abdominal pain. The tube feedings were given for three days. Pain ceased immediately, both subjectively and to abdominal palpation. The purpura disappeared.

CASE 9.—A girl 14 years of age entered the hospital with a history of abdominal pain, hemorrhagic diarrhea and purpura of the skin. These symptoms were alarmingly intensified during her menstrual period. At that time the abdomen was greatly distended, the pain had to be controlled with opiates, there was angioneurotic edema of the face and the diarrhea was greatly intensified. It was found that the purpura was associated with an ascorbic acid level of zero in the blood. Also, the purpura in subsequent menstrual periods failed to occur when the ascorbic acid level of the blood was raised. With tube feedings the abdominal pain improved but did not entirely disappear. Furthermore, the following menstrual period was extremely severe, and the symptoms of pain, abdominal distention, diarrhea and angioneurotic edema reappeared. The unsatisfactory improvement with tube feeding led to the conclusion that the patient had an intrinsic allergy and that she was undoubtedly sensitive to bacteria, her symptoms being intensified with infection. The intensification of the symptoms during menstruation was explained by the possibility of endometriosis in an unusually allergic person.

The case illustrates the value of tube feedings in ruling out sensitization to food in a difficult situation.

The change in the patient's manifestations of allergy when the diet has been administered a few days is of use in estimating the importance of food as an etiologic factor. In some cases the improvement is rapid and dramatic, while in other cases, especially of some types of eczema, progress is slow. However, after a week's use of a synthetic diet one can usually decide fairly accurately the role food is playing in the manifestations of allergy. When no improvement in the symptoms and the physical condition of the patient occurs, food as a factor can be dismissed and the patient returned to his usual diet. The ruling out of the food factor emphasizes the search for the causes in other fields. If improvement indicates that food is to some degree important, such essential foods as wheat, milk and eggs may be added one at a time to the mixture or given by mouth.

USE OF THE DIET FOR PATIENTS WITH TYPHOID

The regulation of the diet continues to be of prime importance to the welfare of the patient with typhoid. Since the work of Shaffer and Coleman [16] the importance of adequate nutrition in typhoid has been recognized, and the studies of Coleman [16] indicate that the clinical course of patients given high caloric diets is more favorable than that of patients subjected to partial starvation. At the present time an extensive clinical and experimental literature has accumulated on the general subject of the effect of nutritional deficiency on resistance to infection,[17] and most of the evidence indicates that the body is more susceptible to infection when the diet is inadequate. Moreover, the evidence suggests that the requirements for calories, protein, thiamine, riboflavin, nicotinic acid and ascorbic acid are increased during infections.

It is generally agreed that a diet for patients with typhoid should be low in residue [18] so as to

16. Shaffer, P. A.: Metabolism in Typhoid Fever, J. A. M. A. **51**:974 (Sept. 19) 1908. Shaffer, P. A., and Coleman, W.: Protein Metabolism in Typhoid Fever, Arch. Int. Med. **4**:538 (Dec.) 1909, Coleman, W.: The Influence of the High Calory Diet on the Course of Typhoid Fever, J. A. M. A. **69**:329 (Aug. 4) 1917.

17. Robertson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**:123, 1934. Perla, D., and Marmorston, J.: Natural Resistance and Clinical Medicine, Boston, Little, Brown & Company, 1941, sect. 7.

18. Paullin, J. E., and Minnich, W. R., in Barr, D. P.: Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, pp. 1212-1220.

minimize work and trauma of an ulcerated intestine. This synthetic diet has almost no residue.

High caloric feeding in practice is found to be difficult, since patients with typhoid have no appetite and little if any desire for food. A great deal of persuasion is needed, and the nurse or dietitian must spend much time, in fact, often hours, persuading the patient to ingest the required number of calories. Since the synthetic diet was given by indwelling stomach tube, the amount of nursing service required for its administration was greatly reduced.

It will be noted that the doses of vitamins given to patients with typhoid were massive and probably in excess of their actual requirements, but the decision to err on the side of too much rather than too little was based on the following considerations: 1. There is indication that the requirements of vitamins are increased in such a toxic febrile state, and the extent of this increase is not known. 2. By the time the diagnosis is made, the patient may have gone for a number of days without adequate food owing to poor appetite and a nutritional deficit may have developed. 3. There may be some question of complete absorption, especially if there is diarrhea.[19] 4. It has been suggested that some of the clinical manifestations of the disease may be due at least partially to vitamin deficiency and not to the toxic aspects of the infection itself. 5. No harm can result from giving amounts greater than the actual requirements.

Eleven patients were given the diet during the summer of 1941, and some of the clinical observations made are summarized in tables 7 and 8. In all but 2 cases, diagnosis was established by positive cultures of stool, blood or both. Five patients gained weight during the time of tube feeding (i. e., febrile period usually). Four patients lost weight (greatest loss of weight, 5½ pounds [2.5 Kg.]). Two were too sick to be weighed. Loss of weight occurred in patients who were obese to begin with. Other forms of treatment consisted of use of sulfonamide compounds, transfusions and convalescent serum. Seven patients had nervous manifestations, such as headache, tremor and stupor. These gradually disappeared as the disease subsided. An important observation was that there was no abdominal distention. One patient had slight transient tympany, and 1 had severe distention on entry which subsided promptly during the first week. There were relapses in 2 patients. Although there was variation in the duration of the fever, this could not be seen to have been changed by the diet.

Vomiting of one or two feedings per twenty-four hours sometimes occurred during the course of the highest febrile period but was rare after defervescence had begun. Patients usually had one or two, occasionally more, fluid greenish stools per day during the febrile period. The daily enema was usually not necessary. Abdominal cramps were rare.

A few patients complained of pain in the throat, substernally or in the abdomen following feedings. These same patients could be fed at night during sleep without being awakened;

TABLE 7.—*Data for Patients with Typhoid*

Patient	Age, Yr.	Sex	Height, In.	Calculated Basal Calories	Days of Tube Feeding	Calories per Day by Tube	Amount per Feeding, Cc.	Weight Before Feeding, Lb.	Weight After Feeding, Lb.
W. K.	19	M	68	1,520	7	3,000	180	107	106
J. N.	11	M	55	1,300	20	2,500	150	61	62½
R. G.	10	M	55	1,260	7	2,500	150	57½	56
A. B.	23	M	68	1,900	7	3,500	210	200	198¾
E. D.	30	F	63	1,300	22	3,000 (12)*	180 (12)	114½	120¼
						3,500 (9)	210 (9)		
G. C.	40	F	63	1,290	23	3,000	180	114	123
†	..	..	..	.....	27	3,000	180	...	121
F. C.	6	M	47	1,075	25	2,083 (12)	125 (12)	37	41¾
						2,500 (13)	150 (13)		
N. K.	35	M	71	1,725	19	3,000 (5)	180 (5)	145	147
						3,500 (14)	210 (14)		
J. J.	33	M	72	1,900	16	3,000	180	195	189½
P. E.	16	F	66	1,660	18	3,000 (16)	180	‡	147½
†	..	..	..	.....	13	3,000	180	...	143
I. B.	61	F	..	.....	28	3,000	180	‡	

* Number of days in parentheses.
† Fed again during a relapse.
‡ Too sick to be weighed.

19. Bean, W. B., and Spies, T. D.: Vitamin Deficiencies in Diarrheal States, J. A. M. A. **115**:1078 (Sept. 28) 1940. Dann, M., and Cowgill, G. R.: Influence of Diarrhea on the Vitamin B_1 Requirement, Arch. Int. Med. **62**:137 (July) 1938.

hence no importance was attached to these symptoms.

The experience with patients with typhoid shows that the synthetic diet can be given successfully and apparently satisfactorily. We were impressed by the fact that there was no significant loss of weight; that often there was a gain. This was found also by Coleman [20] with high caloric diets of natural foods. The absence or rapid disappearance of abdominal distention was also noteworthy. This was attributed to the rapid absorption of dextrose and amino acids elimination of all but a minimum of residue. Because of this the diet appears to merit further trial.

COMMENT

We have not had an extensive experience with the use of this diet for ulcerative colitis, but experience with a patient who has been lately under observation has been impressive. The diet was given through a nasal tube for a period of four weeks. During this time he was extremely ill with high fever and had from sixteen to twenty stools a day. In spite of the great loss of fluid and nutrients, his nutrition was well preserved. Experience of this sort leads us to believe that a synthetic diet of this nature will often prove life saving. We suggest that the fat be kept low and that, as other observers [21] have suggested with regard to protein, the amino acids be fed in amounts from 150 to 200 Gm. a day and dextrose from 300 to 400 Gm. In this patient there was no distention. Undoubtedly high in the intestinal tract, leaving no carbohydrate for fermentation in the lower portion of the tract.

The results for typhoid were good, but they cannot be said to have demonstrated conclusively the superiority of this diet over others now in use in the treatment of this disease, since this would require controls and an extensive study carried over many years. However, the diet does carry out more than any other the two main principles recognized to be important in a diet for typhoid, namely administration of adequate amounts of the various nutritional factors and

TABLE 8.—*Patients with Typhoid*

Patient	Diagnosis and Basis for It	Other Forms of Treatment	Nervous Manifestations	Distention	Complications
W. K.	Paratyphoid B; rising titer	None	None	None	None
J. N.	Typhoid; positive cultures of blood and stool	Transfusion of convalescent blood	Headache before diet; tremor at first	None	Occult blood in the stool
R. G.	Cultures of blood and stool yielded Salmonella enteriditis; typhoid and paratyphoid agglutinins	Sulfaguanidine before entry	None	None	None
A. B.	Typhoid; positive cultures of blood and stool	None	None	None	Pain in the right side of neck
E. D.	Typhoid; positive cultures of blood and stool	Intradermal typhoid vaccine when afebrile	None	Slight transient tympany	Three relapses; tube feeding during the last
G. C.	Typhoid; positive cultures of blood and stool	Transfusion; sulfaguanidine before entry	Tremor of outstretched hands*	None	Relapse
F. C.	Typhoid; positive cultures of stool	Sulfadiazine	Delirium before entry; gradually became rational and cooperative	None	Malnutrition, negativism and refusal of food on entry
N. K.	Typhoid; positive cultures of blood and stool	Convalescent serum	Apprehension; headache	None	Scrotal ulcer; occult blood in stool
J. J.	Typhoid; positive cultures of blood and stool	Sulfathiazole and quinine before entry	Headache	None	Trace of occult blood in stool
P. E.	Typhoid; positive cultures of stool	Transfusions; convalescent serum	Stupor which gradually disappeared	.....	Massive intestinal hemorrhage before feedings were started; relapse; anemia
I. B.	Typhoid; positive cultures of blood and stool	Sulfadiazine	Deep stupor	Severe on entry; subsided gradually in one week	Dyspnea and rales at the lung bases; glossitis

* Headache and mild typhoid state before diet.

20. Coleman, W.: Weight Curves in Typhoid Fever, Am. J. M. Sc. **144**:659, 1912.

21. Mackie, T. T.: The Medical Management of Chronic Ulcerative Colitis, J. A. M. A. **111**:2071 (Dec. 3) 1938. Stickney, J. M.; Heilman, F. R.; Bargen, J. A., and Dearing, W. H.: Sulfaguanidine in Ulcerative Intestinal Diseases, Proc. Staff Meet., Mayo Clin. **17**:33, 1942.

more experience in the use of the diet for various forms of ulcerative colitis will be of interest.

Since much of the fighting during the present war is occurring in tropical regions, the incidence of various types of infectious diarrhea with lesions of the lower part of the intestinal tract is likely to be high. There is a possibility that this diet may prove to be useful under such conditions, especially since its ingredients are desiccated and concentrated to the highest extent.

SUMMARY

A purified diet composed of amino acids, dextrose and emulsified oil to which is added a salt mixture and crystalline vitamins is suggested as of use in three possible conditions: first, for patients with food allergy; second, for patients with severe infections of the intestinal tract, and, third, as a means of determining the requirements for certain of the vitamins.

Our experience with the use of this diet for patients with allergy leads us to believe that it is a useful tool among others to determine whether or not a patient is sensitive to food, at the same time fully maintaining his nutrition. The principles on which the use of the diet rests indicate its usefulness for typhoid and other ulcerative lesions of the lower part of the intestinal tract.

The staffs of Barnes Hospital and of the St. Louis City Isolation Hospital cooperated in these studies.

Progress in Internal Medicine

DISEASES OF THE LIVER AND BILIARY TRACT

HEPATIC INVOLVEMENT IN VARIOUS DISEASES RELATED TO THE WAR

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The global extent of the present war has brought the various aspects of tropical diseases to the attention of members of the medical profession with renewed emphasis. Medical officers with troops are concerned primarily with the acute phases of such diseases. Civilian physicians, on the other hand, will be more interested in the chronic phases, found in soldiers after discharge from the army or brought back to the civilian population by the troops. Numerous articles, such as that of Faust,[1] have reviewed this field and called attention to the public health hazards concerned.[2] In the present review reference will be limited to the evidence of hepatic involvement by these various conditions.

MALARIA

Malaria constitutes the most widespread hazard and the most serious infectious disease for the military forces of the United States. Particularly in the northern and western sections of this country it now is relatively uncommon and most of the patients seen have mild forms. However, it is recognized that enlargement and tenderness of the liver may occur in the course of the disease. Jaundice is one of the cardinal signs in black water fever. Pathologists have long described extensive alteration in the histologic appearances of the liver in fatal cases. The past year Kopp and Solomon [3] have described alteration in the reactions to various functional tests (bromsulphalein, cholesterol, hippuric acid and cephalin flocculation) in cases of therapeutic malaria. These tests showed a return to normal function within three to six weeks.

Greene and Bruger [4] reported that the result of the cephalin flocculation test of Hanger was strongly positive in 2 cases of therapeutic malaria without jaundice. I have personally seen 1 other patient with dementia paralytica in whom benign tertian malaria was induced. Before the course of chills was completed marked icterus developed, with an enlarged and tender liver, and the patient died with the clinical picture of an acute hepatitis and hepatic insufficiency.

More recently Mirsky, von Brecht and Williams [5] have reported a series of 10 cases of malaria. The bromsulphalein test gave a positive result in only 20 per cent of the cases in which it was used. The cephalin flocculation test, on the other hand, gave a positive result in all. Because of this, Mirsky and his associates emphasized the importance of diet and measures to improve the status of the liver during both the acute and the convalescent period of the disease.

INFECTIOUS JAUNDICE

Jaundice has been known since antiquity in both sporadic and epidemic forms. The review of Ottenberg and Spiegel [6] reemphasizes the variety of infectious and chemical agents which may produce hepatic injury and so give rise to this symptom. Weil's disease, or leptospiral jaundice, was the first type of jaundice in which a specific infectious agent was recognized. Yellow fever has been recognized clinically for many years, but the identification of the specific causal virus has been recent.

That acute hepatitis, whether epidemic or sporadic, is a specific infectious disease was stressed by Cockayne [7] and later by Pickles.[8] American epidemics were reported by Hiscock

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1. Faust, E. C.: Disease in the Tropical War Zones, Gastroenterology **1**:995 (Nov.) 1943.

2. Most, H., and Meleney, H. E.: Falciparum Malaria: The Importance of Early Diagnosis and Adequate Treatment, J. A. M. A. **124**:71 (Jan. 8) 1944.

3. Kopp, I., and Solomon, H. C.: Liver Function in Therapeutic Malaria, Am. J. M. Sc. **205**:90 (Jan.) 1943.

4. Greene, C. H., and Bruger, M.: The Functional Study of the Liver and Its Clinical Evaluation, New York State J. Med. **43**:318 (Feb. 15) 1943.

5. Mirsky, I. A.; von Brecht, R., and Williams, L. D.: Hepatic Dysfunction in Malaria, Science **99**: 20 (Jan. 7) 1944.

6. Ottenberg, R., and Spiegel, R.: The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents, Medicine **22**:27 (Feb.) 1943.

7. Cockayne, E. A.: Catarrhal Jaundice, Sporadic and Epidemic and Its Relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. **6**:18, 1912.

8. Pickles, W. N.: Epidemic Catarrhal Jaundice: Outbreak in Yorkshire, Brit. M. J. **1**:944 (May 24) 1930; Epidemic Catarrhal Jaundice, Brit. J. Child. Dis. **33**:192 (July-Sept.) 1936.

and Rogers[9] and by Blumer.[10] More recent epidemics have been reported by Ottenberg and Spiegel[6] in the United States, Ford[11] and Evans[12] in England and Leffkowitz[13] in Palestine.

Of particular interest is the account by Marchand[14] of health conditions in an isolated Indian village in the Yukon territory brought into contact with the outside world by the construction of the new Alaskan Military Highway. The previously healthy village was forthwith swept by epidemics of measles, dysentery, whooping cough, mumps, meningococcic meningitis and catarrhal jaundice. This is evidence both for the infectious nature of the jaundice and for the presence of healthy carriers among the urban workmen brought to the Indian village.

Willcox[15] called attention to the military importance of infectious jaundice in troops during the last war, especially on the eastern front. Military epidemics have been reported in the present war by Cameron.[16] In the majority of these epidemics water, milk and foods apparently could be excluded as sources of infection. Close contact with other persons suffering from the disease was the rule. The incubation period varied from three to five weeks, with an average of twenty-eight to thirty-one days.

The reports of different epidemics vary in details but agree that there is a prodromal period of three to ten days. The prodromata frequently are associated with symptoms in the upper respiratory tract and an initial diagnosis of "grip." This picture has been emphasized by Blumer, by Ottenberg and Spiegel and by Rogers.[17] Cameron and Ford stressed headache, anorexia and irritability. There is abdominal discomfort, which may be so severe as to suggest acute appendicitis or biliary colic. Constipation rather than diarhea is the rule. Fever usually is present during the preicteric stage. Leukopenia is the rule. These prodromal symptoms tend to disappear after the onset of jaundice. The liver usually is enlarged and tender. Splenic enlargement is much less frequent. The jaundice usually clears in one to four weeks.

The epidemic of jaundice associated with the use of human serum in the preparation of yellow fever vaccine was discussed last year.[18] These cases differed from those encountered in ordinary epidemics of infectious hepatitis in the long incubation period. This varied from forty to one hundred twenty days but usually was between seventy and ninety days. The gradual onset with less marked prodromal symptoms, the usual absence of fever and the normal leukocyte count seem further to differentiate this disease from the epidemic type of hepatitis.

Detailed reports of this epidemic to date are limited in number. One of the most extensive is that of Turner and his associates,[19] who studied 4,083 cases, with 14 deaths, occurring at Camp Polk, La. In this group the incubation period varied from nine to twenty-three weeks. The most common symptoms on the patients' admission were anorexia, weakness, nausea, abdominal pain and vomiting. These often preceded the jaundice. Fever was unusual.

Jaundice and enlargement and tenderness of the liver were the most important findings on physical examination. Evidences of a hemorrhagic diathesis were usual when the disease was severe. Slight leukocytosis was the rule.

The most important complications were as follows: 1. Evidences of disturbances in the central nervous system appeared as changes in personality, delirium or severe coarse tremor of the extremities. A restless stupor deepening into hepatic coma was seen in the fatal cases. 2. Petechial hemorrhages in the skin and mucous

9. Hiscock, I. V., and Rogers, O. F.: Outbreak of Epidemic Jaundice Among College Students, J. A. M. A. **78**:488 (Feb. 18) 1922.

10. Blumer, G.: Infectious Jaundice in the United States, J. A. M. A. **81**:353 (Aug. 4) 1923.

11. Ford, J. C.: Infective Hepatitis: Three Hundred Cases in an Outer London Borough, Lancet **1**:675 (May 29) 1943.

12. Evans, P.: Comments on Epidemic of Hepatitis, Brit. M. J. **2**:446 (Oct. 17) 1942.

13. Leffkowitz, M., cited in Infectious Hepatitis in Palestine, Foreign Letters (Palestine), J. A. M. A. **123**:1062 (Dec. 18) 1943.

14. Marchand, J. F.: Tribal Epidemics in the Yukon, J. A. M. A. **123**:1019 (Dec. 18) 1943.

15. Willcox, W.: The Epidemic Jaundice of Campaigns, Brit. M. J. **1**:297 (Feb. 26) 1916.

16. Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. **12**:139 (July) 1943.

17. Rogers, O. F.: Epidemic Hepatitis, Correspondence, J. A. M. A. **123**:1066 (Dec. 18) 1943.

18. Greene, C. H.: Liver and Biliary Tract: A Review of the Literature for 1942, Arch. Int. Med. **71**:563 (April) 1943. Jaundice Following Yellow Fever Vaccination, editorial, J. A. M. A. **119**:1110 (Aug. 1) 1942. The Outbreak of Jaundice in the Army, Medicine and the War, ibid. **120**:51 (Sept. 5) 1942. Fox, J. P.; Manso, C.; Penna, H. A., and Madureira Para: Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68 (July) 1942. Findlay, G. M., and MacCallum, F. O.: Hepatitis and Jaundice Associated with Immunization Against Certain Virus Diseases, Proc. Roy. Soc. Med. **31**:799 (May) 1938. Oliphant, J. W.; Gillian, A. G., and Larson, C. L.: Jaundice Following Administration of Human Serum, Pub. Health Rep. **58**:1233 (Aug. 13) 1943.

19. Turner, R. H.; Snavley, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Especial Consideration of Severe Attacks, Ann. Int. Med. **20**: 193 (Feb.) 1944.

membranes were the commonest complication. Massive gastrointestinal hemorrhage was also seen. The response of the blood prothrombin to treatment with vitamin K was one of the best guides to prognosis. 3. Ascites was reported in 13 cases and sometimes was associated with a high concentration of protein in the ascitic fluid. Turner and his associates expressed the opinion that capillary injury was of greater significance in the development of ascites than was reduction in the plasma protein, though this also showed changes. 4. Renal disturbances were manifested by albuminuria and a defective concentration of the urine. 5. Anemia, commonly macrocytic, was a frequent complication, which usually developed late in the course of the illness.

Turner and his associates pointed out that capillary hemorrhage was the most frequent complication in these cases. They concluded that the capillary hemorrhage together with congestion and stasis in the spleen and other viscera leads to increased hemolysis. The products of this hemolysis together with the products of lysis of damaged hepatic cells lead to disturbances in the functioning of the kidneys as well as of the remaining hepatic tissue. Such a process, in their opinion, explains many of the clinical manifestations reported.

Jaundice has developed after the use of human serum for other conditions. Propert [20] reported on a group of children who received pooled convalescent measles serum and in whom jaundice developed after seventy-eight to eighty-three days. Investigation by the British Ministry of Health [21] showed that 109 persons had been inoculated with this convalescent measles serum. Jaundice developed in 41, with few fatalities.

Jaundice has been reported to occur in soldiers after the prophylactic use of plasma from patients convalescent from mumps. This subject has been reviewed in detail in a report of the British Ministry of Health.[22] Reference was made there to 12 reported cases of jaundice in persons who had previously been given transfusions of plasma or of whole blood. Beeson [23] reported 7 cases of jaundice developing thirty-three to one hundred and nineteen days after transfusion of pooled plasma or of citrated blood. Morgan and Williamson [24] followed up a series of 50 patients who had received serum or dried plasma. Jaundice developed in 9 of these patients (18 per cent) after forty-nine to one hundred and seven days. The extremely high incidence of jaundice in this series emphasizes the need for a careful and prolonged follow-up of patients receiving plasma or blood by transfusion.

In the past, attempts at experimental transmission of infectious hepatitis have been unsuccessful. Cameron [16] and Van Rooyen and Gordon [25] administered bile, gastric washings and blood from patients with jaundice by a variety of routes to a variety of animals without being able to reproduce the disease.

Lainer [26] administered blood or bile from patients with sporadic catarrhal jaundice to a series of 15 healthy subjects. No evidence of jaundice or of hepatitis appeared in any of them. Voegt [27] administered duodenal juice from a patient with epidemic hepatitis orally to each of 4 human volunteers. Serum, plasma or hemolyzed erythrocytes from patients were injected into 6 other volunteers. In 6 of these recipients subclinical icterus or other signs of hepatic impairment developed. Findlay and Martin [28] produced jaundice in 3 human volunteers by instilling into the nares nasal washings from patients in the preicteric or early icteric stage of jaundice following injection of yellow fever vaccine. Symptoms appeared in the volunteers after twenty-eight, thirty and forty days. A report [29] has also been made to the effect that a virus has been cultivated from the duodenal fluid of patients with epidemic hepatitis.

Andersen,[30] of Copenhagen, noted that epidemics of hepatitis, contrary to most epidemics, had a greater case incidence in country villages

20. Propert, S. A.: Hepatitis After Prophylactic Serum, Brit. M. J. **2**:677 (Sept. 24) 1938.

21. McNalty, A. S.: Annual Report of the Chief Medical Officer, Ministry of Health, for the Year 1943, London, His Majesty's Stationery Office, 1938, p. 38.

22. Homologous Serum Jaundice, Memorandum Prepared by Medical Officers of the Ministry of Health, Lancet **1**:83 (Jan. 16) 1943.

23. Beeson, P. B.: Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma: Report of Seven Cases, J. A. M. A. **121**:1332 (April 24) 1943.

24. Morgan, H. V., and Williamson, D. A. J.: Jaundice Following Administration of Human Blood Products, Brit. M. J. **1**:750 (June 19) 1943.

25. Van Rooyen, C. E., and Gordon, I.: Some Experimental Work on Infective Hepatitis in M. E. F., J. Roy. Army M. Corps **79**:213 (Nov.) 1942.

26. Lainer, F.: Zur Frage der Infektiosität des Ikterus, Wien. klin. Wchnschr. **53**:601 (July 26) 1940.

27. Voegt, H.: Zur Aetiologie der Hepatitis epidemica, München. med. Wchnschr. **89**:76 (Jan. 23) 1942.

28. Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization: Transmission by Intranasal Instillation, Lancet **1**:678 (May 29) 1943.

29. Siede, W., and Luz, K.: Zur Aetiologie der Hepatitis epidemica, Klin. Wchnschr. **22**:70 (Jan. 23) 1943.

30. Andersen, T. T.: Etiology of Hepatitis Epidemica (Epidemic Jaundice), Acta med. Scandinav. **93**:209, 1937. Andersen, T. T., and Tulinius, S.: Etiology of Hepatitis Epidemica (Epidemic Jaundice), ibid. **95**:497 1938.

than in urban communities. Jaundice occurs in epidemics in pigs, and he was able to transfer the disease of pigs through four generations in young pigs by feeding infected livers. He also produced jaundice in pigs by feeding 50 cc. of duodenal bile from human patients with jaundice. The incubation period was short, only three to four days. Blumer [31] reported 2 cases of febrile jaundice occurring within five days after the patients had eaten roast pork.

It is generally accepted at the present time [32] that the infectious nature of epidemic hepatitis has been established. Experiments in its transmission suggest that it is due to a virus, while differences in the reported incubation periods and in the clinical pictures suggest that there are several viruses which may produce jaundice. The period of greatest infectivity apparently is during the prodromal and preicteric stages of the disease, and the infectivity may be lost shortly after clinical jaundice becomes manifest. Children are more susceptible than adults, and only a small proportion of the adults in an urban population are susceptible. Failure to recognize these relationships may be responsible for some of the difficulty in the experimental transmission of the disease.

Rapid, simple clinical methods for the recognition of these hepatotoxic viruses would do much to clarify the etiology and diagnosis of hepatitis and jaundice.

ASPIRATION BIOPSY OF THE LIVER

The study of specimens of liver obtained by the routine postmortem use of the viscerotome has been of great value in determining the incidence and extent of infection with yellow fever in South America.

Similar studies by Roholm and Iversen [33] by means of aspiration biopsy of the liver have done much to clear up the pathologic picture of acute hepatitis.[34] "Catarrhal jaundice" as used by Virchow [35] to indicate obstruction of the common duct in the course of a "duodenal catarrh," is now generally accepted as a misnomer. Opportunities for pathologic examination of the liver in cases of this condition have been few. In this country Klemperer, Killian and Heyd [36] were the first to emphasize the existence of parenchymal lesions in the liver. Barber and Osborn [37] and Findlay and Dunlop [38] have recently reported cases of simple jaundice in which they demonstrated the presence of acute necrosis of the liver.

Roholm and Iversen have made routine aspiration biopsies of the liver in a series of 26 cases of sporadic jaundice. They inserted a cannula into the liver in the right ninth interspace at the posterior axillary line. By means of a record syringe pieces of liver 1 to 2 cm. long and 2 mm. in diameter were aspirated. They found disarrangement of the hepatic cells with necrotic changes, especially in the centers of the lobules. There were mononuclear cell infiltration and increase of connective tissue around the portal spaces and in some of the lobules.

These studies of Roholm and Iversen have been extended by Dible, McMichael and Sherlock [39] in a series of 56 cases of acute hepatitis, 14 of them cases of epidemic hepatitis. The jaundice followed arsenotherapy in 35. In the remainder the jaundice followed prophylactic use of mumps convalescent serum or transfusion of serum. In all they found degenerative, necrotic or autolytic changes in the hepatic cells, especially in the center of the lobules. Repeating the biopsy after recovery showed that in some cases there was complete restitution and that in others acute or subacute necrosis (atrophy) or occasionally mild fibrosis or cirrhosis resulted. In no case was there evidence of bile stasis, which is claimed to occur in catarrhal jaundice. The lesions in the liver were similar in all the groups of cases studied, but this is not to be taken as proof of a common causation of the different types of jaundice.

31. Blumer, G.: Note on Relationship Between Jaundice in Pigs and Jaundice in Human Beings, J. Mt. Sinai Hosp. **8**:418 (Jan.-Feb.) 1942.

32. Infective Hepatitis in the War, Foreign Letters (London), J. A. M. A. **121**:879 (March 13) 1943. Catarrhal and Human Serum Jaundice, editorial, ibid. **122**:746 (July 10) 1943. Problem of Infectious Jaundice, editorial, ibid. **122**:1186 (Aug. 21) 1943. Epidemic Hepatitis or Catarrhal Jaundice, editorial, ibid. **123**: 636 (Nov. 6) 1943. Dietrich, S.: Der sogenannte katarrhalische Ikterus und die Hepatitis epidemica, Deutsche med. Wchnschr. **68**:5 (Jan. 2) 1942. Gutzeit, K.: Icterus infectiosus, München. med. Wchnschr. **89**: 185 (Feb. 27) 1942.

33. Roholm, K., and Iversen, P.: Changes in the Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, Arch. path. et microbiol. Scandinav. **16**:427, 1939.

34. Problems of Infectious Jaundice, editorial, J. A. M. A. **122**:1186 (Aug. 21) 1943.

35. Virchow, R.: Ueber das Vorkommen und den Nachweis des hepatogenen, insbesondere das katarrhalischen Icterus, Virchows Arch. f. path. Anat. **32**: 117, 1865.

36. Klemperer, P.; Killian, J. A., and Heyd, C. G.: The Pathology of "Icterus Catarrhalis," Arch. Path. **2**:631 (Nov.) 1926.

37. Barber, H., and Osborn, G. R.: Morbid Anatomy of Sporadic Cases of Infective Hepatic Jaundice, J. Path. & Bact. **49**:581 (Nov.) 1939.

38. Findlay, G. M., and Dunlop, J. L.: A Fatal Case of Acute Necrosis of the Liver Associated with Epidemic Catarrhal Jaundice, Brit. M. J. **1**:652 (April 9) 1932.

39. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, Lancet **2**:402 (Oct. 2) 1943.

Roholm and Krarup,[40] on the basis of clinical and biopsy studies, advanced the view that arsphenamine jaundice is nothing more than epidemic hepatitis in cases in which the resistance of the liver to the virus has been reduced by the arsphenamine. Similar views have been suggested by Bergstrand.[41] The relation of arsphenamine to hepatic disease and jaundice has been a debated topic for many years. Stokes, Ruedemann and Lemon[42] in 1920, for example, expressed views similar to those here reported. This question apparently will not be settled till it becomes possbile to determine the role of virus infection in hepatic disease with assurance. The failure so far to isolate a virus from the liver in cases of epidemic jaundice or jaundice due to serum may be due to the fact that autopsy material has been used and that the virus has disappeared from the liver by the time of death. Watson[43] pointed out that aspiration biopsy early in the course of the disease may provide a means of recovering a virus.

Swedish investigators[44] have reported on aspiration biopsy in hundreds of cases and in a variety of hepatic diseases. They have insisted that it is a harmless procedure. Care must be taken in the selection of cases. The prothrombin time of the blood must be normal, to guard against postoperative hemorrhage. Complete biliary obstruction must be excluded, for injury to a bile duct in the presence of such obstruction may lead to the development of a biliary fistula. Cholangitis, hepatic abscess or other source of infection must be avoided. An improved biopsy needle has been reported by Tripoli and Fader.[45] Even under these conditions Watson reported that in many cases (40 per cent) it is difficult to obtain satisfactory specimens. Once this difficulty is surmounted it may be expected that hepatic biopsy will be more widely used in the future.

40. Roholm, K., and Krarup, N. B.: Die Histopathologie der Leber bei sogennanten Salvarsanikterus mittels Aspirationsbiopsie untersucht, Arch. f. Dermat. u. Syph. **181**:521, 1940.

41. Bergstrand, H.: Ueber die akute und chronische gelbe Leberatrophie mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930.

42. Stokes, J. H.; Ruedemann, R. J., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, Arch. Int. Med. **26**:251 (Nov.) 1920.

43. Watson, C. J.: Personal communication to the author.

44. Iverson, P., and Roholm, K.: On Aspiration Biopsy of the Liver, with Remarks on Its Clinical Significance, Acta med. Scandinav. **102**:1, 1939.

45. Tripoli, C. J., and Fader, D. E.: The Differential Diagnosis of Certain Diseases of the Liver by Means of Punch Biopsy, Am. J. Clin. Path. **11**:516 (June) 1941.

LEPTOSPIRAL JAUNDICE (WEIL'S DISEASE)

In the first World War many cases of Weil's disease were described.[46] If trench warfare returns in the present conflict and troops again live in wet, rat-infested trenches, the number of cases of leptospiral jaundice will increase. Reports of such cases to date have been rare.[47]

Clapper and Meyers[48] reported 13 cases of Weil's disease in civilians and emphasized the clinical and laboratory evidence of meningitis and of cardiac damage present in addition to the jaundice and hepatic damage. Bruno, Wilen and Snavely[49] reviewed 15 cases observed in New Orleans between 1939 and 1941. They stressed the fact that the diagnosis is frequently missed and that the disease probably is much more common than indicated by published reports.

The clinical features of diagnostic significance are: (1) an acute infectious disease with sudden onset, fever, headache and prostration; (2) severe myalgia appearing spontaneously or on pressure in the thighs, calves and back; (3) signs of hepatic damage; (4) signs of renal damage; (5) leukocytosis; (6) epidemiologic information as to exposure or occupation. The authors reemphasized that if any four of these features are present the diagnosis of Weil's disease should be considered.

Bruno and his associates stressed the meningeal and cardiac features seen in many cases. They pointed out that a hemorrhagic diathesis is present in many. This presumably is due to a toxic effect of the leptospiras on the capillary wall, for normal prothrombin values were found in cases in which there were hemorrhagic changes. They also reported 4 cases in which bronchopulmonary features led to the condition's initially being mistaken for hepatitis secondary to pneumonia or resulting from treatment with a sulfonamide compound.

The diagnostic value of specific agglutinins against Leptospira icterohaemorrhagiae is generally recognized. Bruno and his associates reported 1 case in which the agglutinins in the blood were lost within three years after the patient's recovery. This is not necessarily the

46. Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ., League of Nations **8**:143, 1939. Greene, C. H., and Farrell, E.: Liver and Biliary Tract: A Review for 1939, Arch. Int. Med. **65**:847 (April) 1940.

47. Varadi, S.: Weil's Disease in an Army Camp: Case Report, Brit. M. J. **1**:126 (Jan. 30) 1943.

48. Clapper, M., and Meyers, G. B.: Clinical Manifestations of Weil's Disease with Particular Reference to Meningitis, Arch. Int. Med. **72**:18 (July) 1943.

49. Bruno, F. C.; Wilen, C. J. W., and Snavely, J. R.: Spirochaetal Jaundice: A Report on Fifteen Cases, Including Two Cases of Leptospira Canicola Infection, J. A. M. A. **123**:519 (Oct. 30) 1943.

case, for Packchanian and Tom [50] reported 8 cases in which agglutinins were present in the blood from two to over twenty years after recovery from Weil's disease.

Larson [51] reported the preparation of a specific immune serum which was of value in treating mice infected with Weil's disease. This serum was effective up to the third day of infection but was ineffective after the sixth day. More work must be done before the serum is available for clinical use. The need for early administration, moreover, will in many cases lessen its clinical usefulness.

Of even greater interest is the report by Heilman and Herrell [51a] that penicillin is of value in the treatment of guinea pigs infected with Weil's disease.

HEPATIC CIRRHOSIS IN MANSON'S SCHISTOSOMIASIS

Hepatic cirrhosis is the end result of infection with Manson's schistosomiasis. The clinical features of the condition have recently been reviewed by Koppisch [52] and Villela.[53] Koppisch pointed out that Manson's schistosomiasis is a disease of extended geographic distribution and of great importance as a cause of chronic illness and death within those regions. Africa, northern South America and the Caribbean region are the great endemic foci. In northern Africa it is found in the lower Nile Valley, particularly in the Delta, and in the Sudan. It is present along the East African coast from Zanzibar to below the Zambesi River. It occurs throughout parts of Tanganyika, the Belgian Congo and Rhodesia. In West Africa it is seen in Senegal and French Guinea. There is a small endemic focus in Yemen, Arabia. It was estimated in 1937 that in Egypt alone there were 3,000,000 cases of Manson's schistosomiasis.

In the New World it occurs in parts of northern and northeastern Brazil, with a variable incidence, which in one locality has reached 85.18 per cent. In Venezuela its distribution seems to be restricted to a limited part of the north central zone, where 60 to 80 per cent of the population in the valleys near Caracas are infected. The disease is fairly common in Dutch Guiana. In Puerto Rico, 14.6 per cent of the autopsies performed in San Juan, a nonendemic center with a population of about 170,000, have shown evidences of the disease. Its incidence is greatest among persons in the second and third decades of life. It ordinarily affects members of the two sexes to about the same extent.

For the completion of the parasite's life cycle a specific intermediate molluscan host is necessary. Given suitable climatic and hydrographic conditions, a miracidium is hatched when the human feces containing ova of Schistosoma mansoni reach the water. It swims about until it finds a snail of the appropriate species, which it parasitizes. Within the snail the miracidium undergoes morphologic alterations and great multiplication, resulting, at the end of twenty-two to thirty-one days, in the emergence of large numbers of fork-tailed cercarias. The disease is acquired through exposure to cercarias, usually while a person is bathing in an infected stream or working in an irrigation canal, but infection can also take place through the buccal mucosa while one is drinking.

Spread of the disease can be avoided by: (1) curing all who are affected with it, so that no more viable ova will pass with their feces; (2) preventing the contamination of bodies of water with human excreta; (3) exterminating the snails or cercarias, and (4) keeping people away from the sources of infection. One or more or all of these methods may be applicable with success in a few communities, particularly in small ones, but in the larger endemic foci the density of the population and the extent of the infested territory make these methods impractical at the present time.

The usual route of penetration is through the skin. Since the metacercarias are next found in the lung, it is clear that in the derma they must enter either lymphatics or veins. In man they are supposed to enter the veins.

The course followed by the metacercarias seems at all times to be strictly intravascular. Those which are not caught and destroyed in the pulmonary circulation reach the left side of the heart, whence they are ejected with the arterial blood to all organs and tissues. Those which reach organs and tissues whose venous drainage is by way of the portal vein seem to be the only ones that survive and establish a foothold in the mammalian host. By passing from the arterial to the venous side in organs like

50. Packchanian, A., and Tom, N.: Persistence of Leptospira Antibodies in Circulating Blood of Patients Recovered One to Over Twenty Years from Weil's Disease, J. Immunol. **46**:263 (May) 1943.

51. Larson, C. L.: Treatment of Young White Mice Infected with Leptospira Icterohemorrhagiae with Immune Serum, Pub. Health Rep. **58**:10 (Jan. 1) 1943.

51a. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Leptospirosis Icterohemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clinic **19**:89 (Feb. 23) 1944.

52. Koppisch, E.: Manson's Schistosomiasis, J. A. M. A. **121**:936 (March 20) 1943.

53. Villela, E.: Hepatic Lesions in Infections by Schistosoma Mansoni, J. A. M. A. **122**:690 (July 3) 1943; Contribuicao ao estudo histopatologico do figado no Schistosomose mansoni humana, Hospital, Rio de Janeiro **23**:345 (March) 1943.

the spleen, pancreas, liver, stomach and small and large intestine, they reach intrahepatic portal branches, where they attain maturity.

It is probable that in man most of the damage is accomplished by the ova. The characteristic mode of reaction of the tissues in all organs to the presence of these structures is by the formation of a pseudotubercle. The presence of ova leads to progressive fibrosis of portal spaces and of the submucosa of the colon, with ultimate development of a portal cirrhosis and splenomegaly if ova continue to be deposited in sufficient numbers over several years. As part of the cirrhosis there is portal obstruction, resulting in development of a collateral circulation, of which an important complication is the formation of esophageal varices that not infrequently give rise to fatal hemorrhage. The heightened blood pressure in the splenic vein favors the development of sclerotic changes in its wall, at times with calcification, and in a few cases thrombosis supervenes.

The manifestations of the disease, both clinical and anatomic, may conveniently be grouped into three stages: (1) an early period, comprising penetration of the cercarias, migration within blood vessels and maturation in intrahepatic portal branches; (2) an intermediate period, of progressive accumulation of ova in various organs and tissues, and (3) a late period, of frank visceral damage, mainly cirrhosis and splenomegaly.

In man this early period usually is asymptomatic, except for itching for a few hours over the parts exposed to the infested water. A history of well defined itching following a person's falling into, or bathing in, a stream should always bring to mind this disease, and if the stream is known to be infested such a history should be taken as strong presumptive evidence of infection's having actually taken place. Some patients complain of anorexia, weakness, loss of weight, headache, nausea, vague intestinal symptoms, looseness of the bowels and either feverishness or short accessions of high fever. These symptoms have their onset a few days to two weeks after exposure, and not all of them may be present at a given time. Unfortunately, these manifestations have so far been studied in but few cases, and, furthermore, it seems probable that they are present in the heavier infections only. Before ova begin to pass with the feces, there are no sure means of establishing the diagnosis.

The intermediate stage is taken to begin with the onset of oviposition, on or about the fortieth day after exposure. By this time wandering through the body has come to an end, and the worms have reached maturity. The first well defined symptoms of this stage are accompanied by an abrupt onset with fever, accompanied or not by a chill, with a remittent or intermittent course and the temperature reaching 102 or even 104 F. daily. The duration is at least two or three weeks, probably longer when not cut short by treatment with fuadin. The fever is accompanied by the usual symptoms of a febrile process, by generalized or localized abdominal discomfort, with or without pain, which may be colicky, by nausea, vomiting, abdominal distention, dysentery, urticaria and cough, which can be hacking and persistent. Physical examination may disclose patchy areas suggestive of bronchopneumonia and enlargement of the spleen and liver. There may be a severe eosinophilia with a low, normal or elevated leukocytic count.

Frequently there is nothing very characteristic about the disease during the early part of this stage, and the spleen and liver may not be palpable for a number of years after the onset. However, given a case with the geographic possibility of infection, diarrhea with blood in the stools and obscure abdominal symptoms, this disease must be included in the differential diagnosis. In the earlier stages of the disease eosinophilia is frequent, and its presence is of great value in calling the observer's attention to a parasitic illness. Not enough emphasis can be laid on the importance of establishing the diagnosis at this stage, and the earlier the better. Failure to do this and to carry on treatment with fuadin will seal the patient's fate or condemn him to prolonged ill health.

In the late stage the clinical picture is dominated by the manifestations of cirrhosis with splenomegaly, ascites, anemia and cachexia. Diarrhea may still occur in bouts, but it may be absent for long periods. Vague abdominal symptoms and pain of variable intensity referred to some part of the colon usually persist. At any time during this stage there may come accessions of fever lasting from a few days to several weeks. Eosinophilia may persist in some cases, while in others it is lacking. Ova are often absent from the stools, mainly owing to the fact that the disease has lasted for many years and the number of ovipositing worms has become greatly reduced. The clinical picture may be the exact duplicate of Laennec's cirrhosis,[53a] or it may mimic the Banti syndrome when there is anemia

53a. Jaffe, R.: Was lehrt uns die Bilharziazirrhose in bezug auf die Probleme der Leberzirrhose, Schweiz. med. Wchnschr. **72**:1149 (Oct. 17) 1942; General Considerations on Pathogenesis: Syphilitic Aortitis, Myocarditis, Hepatic Cirrhosis, J. Lab. & Clin. Med. **29**:139 (Feb.) 1944.

with leukopenia. Hematemesis is of frequent occurrence and may be the first indication of cirrhosis; not infrequently it is the immediate cause of death. The diagnosis at this stage depends on the clinical history, on the presence of eosinophilia, on repeated search for ova in the stools by means of methods of concentration and, lastly, on exploratory laparotomy with biopsy of the liver.

Once cirrhosis is well developed, it is probable that the establishment of the diagnosis becomes of little more than academic interest. Certainly, some symptoms, like those of colitis, may be favorably influenced by judicious treatment even in the presence of far advanced cirrhosis, but practically no effect will be exercised on the hepatic process, which will continue to progress relentlessly even after the parasites are destroyed.

The liver may be large, small or of normal size. It is always dense and pale, with a surface that is usually finely nodular and only exceptionally coarsely nodular. On section the principal characteristic is the concentration of the fibrosis about the larger portal branches. When this feature is well developed there are distinct collars of white or pink connective tissue about these veins—the so-called pipestem type of cirrhosis. Microscopically, there is diffuse scarring of the portal spaces, with formation of pseudotubercles about ova, diffuse and focal infiltration with lymphocytes, plasma cells and eosinophils and more or less pigmentation of the Kupffer cells and phagocytes in the periportal tissues with finely divided brown pigment.

The spleen may not be enlarged, even when there is advanced cirrhosis, but this is exceptional, splenomegaly being the rule. In the late stage the spleen is characterized by a diffuse fibrosis of the pulp, which ultimately results in great reduction in the number of cells in the cords and a diminution in the size and number of lymphoid follicles. Brown pigment is usually found in the reticuloendothelial cells of the organ.

The ultimate cause of death is hematemesis due to a ruptured esophageal varix in one third of the advanced fatal cases, cachexia due to cirrhosis in another third and complications in the remainder. The studies of Koppisch show that schistosomiasis is the cause of hepatic cirrhosis in fully one third of the cases encountered in Puerto Rico. Because of the characteristic pathologic picture, aspiration biopsy, if feasible in such cases, would seem to be of value in differential diagnosis, as Villela has emphasized the importance of postmortem viscerotomy in the study of the epidemiology of this disease.

AMEBIC HEPATITIS AND HEPATIC ABSCESS

Amebic dysentery is one of the most important of the tropical diseases which may be expected to be of military and postwar significance. A discussion of amebic dysentery is without the scope of this review. Its chief complication, amebic hepatitis and hepatic abscess, has been the subject of a comprehensive review by Ochsner and DeBakey.[54] In this monograph they present an analysis of 181 personal cases together with a review of the literature containing over 400 references.

Ochsner and DeBakey began by pointing out the fallacy in considering amebiasis a tropical disease. Endamoeba histolytica is ubiquitous and has been found in all parts of the world. While it has been generally accepted that 5 to 10 per cent of the population in this country harbor the parasite, recent surveys suggest that the true average incidence may be as high as 20 per cent.

The incidence of hepatic complications in cases of intestinal amebiasis varies greatly, depending on the material studied. According to Ochsner and DeBakey it is approximately 4 to 5 per cent. On the basis of these figures they calculated that 20,000,000 to 25,000,000 people in this country are infected with pathogenic amebas and that the potential number with hepatic complications is approximately 1,000,000. The importance of this problem, especially from the standpoint of public health, is obvious.

Curiously, sex is an important factor in the development of this condition, for 83.9 per cent of patients with intestinal amebiasis are males, and 86.7 to 95.1 per cent of those in whom the hepatic complications develop are males. Most of the patients were seen in the third, fourth and fifth decades of life.

In the pathogenesis of amebic hepatitis it is agreed that amebas reach the liver from the primary focus in the intestine through the portal vein. There they lodge in the smaller portal radicles, where they produce thrombosis with infarction and consequent focal necrosis. These areas characteristically appear in the portal spaces and extend peripherally toward the capsule, thus paving the way for the cytolytic activity of the amebas to produce lysis and destruction of the involved hepatic parenchyma. In this early phase of amebic hepatitis a balance exists between regression toward healing, with replacement by scar tissue, and progression toward suppuration and abscess. The balance between these

54. Ochsner, A., and DeBakey, M.: Amebic Hepatitis and Hepatic Abscess: An Analysis of One Hundred and Eighty-One Cases with Review of the Literature, Surgery **13**:460 (March); 612 (April) 1943.

two processes is determined by such predisposing factors as the relative resistance of the host and the virulence and number of the invading amebas. The presence of pathogenic bacteria, alcohol, trauma and other detrimental agencies also contributes to the formation of an abscess.

The typical abscess is filled with the characteristic chocolate sauce pus. Amebas may be found in the pus but are more frequently found in the cecum and ascending colon. Venous blood from this area drains through the superior mesenteric vein to the right lobe of the liver. This apparently explains why the majority of abscesses are single (65 to 88.6 per cent) and occur in the right lobe of the liver (84.7 to 96.3 per cent).

The clinical manifestations at the onset of hepatic abscess vary considerably. Usually they come on early, in the first three months of the course of an amebic dysentery, but may be acute, subacute or insidious in development. The most important systemic manifestation of hepatitis or abscess was fever, which usually was of low grade and intermittent. This was present in 84.5 per cent of the cases. Weakness, loss of weight, anorexia, diarrhea, chills and profuse perspiration, nausea and vomiting were less frequently observed. Jaundice was observed in 10.5 per cent of the cases. Diarrhea was present in 25.4 per cent of the cases, and a history of antecedent diarrhea could be obtained in only 67.2 per cent of these cases.

The earliest and most constant local manifestations of amebic hepatitis are pain and tenderness in the region of the liver. This was present in 86.7 per cent of the cases. Clinically recognizable enlargement of the liver was present in 72.9 per cent.

Laboratory findings include a moderate leukocytosis with an average count of 16,460 in this series. The majority of the patients showed a secondary anemia, which was more pronounced in those with chronic involvement. The frequency with which amebas are demonstrated in the stools varies with the technic of the examiner and the number of examinations made. Ochsner and DeBakey reported that amebas were found in 36.4 per cent of their cases.

Roentgenography is one of the most important and dependable laboratory procedures in the diagnosis of amebic abscess of the liver. The elevation and immobility of the diaphragm frequently are characteristic. In cases of uncomplicated abscess of the liver a distinct bulging of the diaphragm may be observed pointing upward into the lower pulmonary field in both the anteroposterior and the lateral roentgenograms. A positive diagnosis was made by roentgenography in from 69 to 100 per cent of the cases, depending on the particular series reported. Ochsner and DeBakey reported a positive diagnosis in 88 per cent of their cases.

The diagnosis of amebic hepatitis and hepatic abscess is not difficult if the conditions are kept in mind and the clinical manifestations and results of laboratory examinations accorded due consideration. An amebic hepatitis should always be considered when a patient has low grade daily remittent or intermittent fever, pain and tenderness over the liver, moderate leukocytosis without a concomitant proportionate increase in polymorphonuclear leukocytes and E. histolytica in the stools. Such a clinical picture during or shortly after an attack of amebic dysentery more strongly indicates the presence of amebic hepatitis. However, it should be realized that even in the absence of intestinal manifestations the condition should be considered, repeated examinations of stools should be done and every attempt should be made to confirm or exclude the diagnosis of amebic hepatitis. The significance of early recognition of this condition has been emphasized repeatedly and lies in the fact that the institution of appropriate therapy during this presuppurative stage may prevent progression to abscess formation.

Whereas there is some variation in the clinical manifestations of amebic abscess of the liver depending on the chronicity of the process, persistent hepatomegaly, pain and tenderness over the hepatic area with occasional radiation to the shoulder, and a daily remittent or intermittent fever of moderate degree are fairly constant manifestations. The presence of these symptoms and signs should always suggest the possibility of an amebic abscess. Anorexia, loss of weight and strength, nausea and vomiting, profuse perspiration and disturbed slumber are less constantly observed, but their presence lends further support to the diagnosis. The presence of an antecedent dysentery is confirmatory evidence, but its absence is not refutatory. It will be recalled that from one third to almost one half of the patients gave no history of a previous dysentery. The diagnosis is supported further by a mild leukocytosis without a disproportionate increase in polymorphonuclear leukocytes. If, in addition to such a clinical picture the characteristic fluoroscopic and roentgenologic findings previously described are present, the diagnosis of amebic hepatic abscess is justified. The demonstration of active or encysted forms of E. histolytica is corroborative evidence, but their absence does not exclude the diagnosis.

It must be realized, of course, that whereas these findings justify the diagnosis of amebic hepatic abscess, its establishment depends on the

demonstration of the characteristic chocolate sauce pus. Herein lies the diagnostic importance of exploratory aspiration. However, the procedure should not be performed without thorough cognizance of its possible dangers. Of these the most important are (1) hemorrhage and (2) extension of infection. Various investigators have directed attention to the possibility of hemorrhage and have reported cases in which this dangerous complication followed exploratory aspiration of an amebic abscess of the liver. The danger of hemorrhage may be almost entirely avoided by administering emetine for several days preceding the aspiration and thus controlling the associated hepatitis. Extension of infection is another danger which deserves special consideration, since it is not always possible to determine clinically whether an amebic hepatic abscess is sterile or contains pyogenic organisms. The latter possibility should always be assumed and the aspiration performed in such a manner that an uninvolved portion of the peritoneum or the pleural cavity is not traversed by the aspirating needle. Obviously this is not always possible, but it should be kept in mind during the attempted aspiration. It should be realized also that this is not as difficult in the presence of an enlarged liver containing an abscess as under normal conditions, for with the former the anatomic relationships have been changed.

These hazardous possibilities, hemorrhage and extension of infection, may be avoided largely by preaspiration therapy with emetine, the type of needle employed, the technic of aspiration and the performance of the procedure in the operating room under absolutely aseptic precautions. Emetine hydrochloride should be administered for at least two to four days prior to aspiration in 1 grain (0.06 Gm.) doses daily. By employing a needle not longer than 10 cm. with a caliber not greater than 2 mm. the danger of puncturing a large vessel is minimized. Ochsner and DeBakey expressed preference for a short, beveled needle or a trocar type with a short, fairly blunt point. The procedure should always be performed in the operating room, first, because aseptic precautions are likely to be greater and, second, because if the abscess is found to be secondarily infected open drainage can be done immediately. The latter possibility can be readily determined by making an immediate smear of the aspirated pus, which will reveal on microscopic examination the presence of large numbers of bacteria and leukocytes in cases in which secondary infection is present. Whereas general anesthesia can be employed, local infiltration analgesia with 1 per cent procaine hydrochloride solution is preferable. Nicking the skin at the contemplated site of puncture with a bistoury will facilitate insertion of the needle.

The cutaneous site of puncture and the direction of the introduction of the needle depend largely on the clinical and roentgenologic findings. Accordingly, in the presence of localizing signs and pointing of the abscess the needle should be introduced directly over the mass or at the site of greatest tenderness. However, if no localizing signs are present the roentgenograms may be of guiding significance. Thus in a case in which the lateral roentgenogram demonstrates the abscess in the anterior portion of the liver the needle may be inserted just below the anterior costal margin about 5 to 6 cm. lateral to the midline and directed superiorly and posteriorly. On the other hand, if the lateral roentgenogram reveals posterior localization of the abscess the needle should be introduced below the costophrenic angle and directed superiorly and anteriorly. However, in those cases in which the abscess is located more anteriorly near the dome of the liver, as occurs most frequently, avoidance of the pleural and peritoneal cavities may be accomplished best by inserting the needle in the ninth or tenth intercostal space in the anterior axillary line and directing it superiorly, medially and slightly posteriorly. Occasionally it may be necessary to puncture the liver in several different directions before pus is encountered. If multiple punctures are necessary it is extremely important to remove the needle entirely before reintroducing it in a different direction rather than changing its direction while the needle is still at its original site. In this way extensive injury to the friable parenchyma of the liver may be prevented. Yater [55] has emphasized the value of hepatosplenography with colloidal thorium dioxide when an abscess in the liver cannot be localized by ordinary roentgenograms.

The treatment of hepatic abscess in the past may be divided into three main periods: 1. The first was the period of purely medical treatment, during which evacuation of the purulent collection was allowed to take place spontaneously. The mortality during this period, which embraced the history of medicine up to the sixth decade of the eighteenth century, was 80 per cent. 2. The second epoch may be said to be limited to the short period from 1860 to the early 1870's, during which early exploration with the aspirator gradually

55. Meredith, R. H.; Cooper, L. F., and Yater, W. M.: Thorotrast Hepatosplenography as Diagnostic Aid in Solitary Liver Abscess: Report of Four Cases, M. Ann. District of Columbia **11**:382 (Oct.) 1942. Yater, W. M., and Coe, F. O.: Ten Years' Experience with Thorotrast Hepatosplenography, Ann. Int. Med. **18**:350 (March) 1943.

became the rule of practice, to be followed by repeated explorations and finally cautious opening with trocars or caustic pastes or by means of small incisions. 3. The third period begins with the 1870's, when the Listerian discovery made surgeons bolder in opening the peritoneal and pleural cavities in an effort to evacuate the abscess early. During this period the trocar gradually yielded to the knife and the rule of surgical practice consisted of immediate evacuation by free incision regardless of situation or quantity of pus. That the mortality during this period was still extremely high is shown by the report on 182 patients admitted to the Charity Hospital in New Orleans during the ten year period 1884 to 1894, among whom there were 87 (or 42.56 per cent) deaths. 4. The combination of treatment with emetine plus aspiration may be considered as inaugurating the fourth, and most important, period in the treatment of amebic hepatitis and hepatic abscess.

Emetine is preferably administered subcutaneously as emetine hydrochloride in daily doses of 0.065 Gm. (1 grain) until 0.39 to 0.65 Gm. (6 to 10 grains) has been given. Because of its toxicity in excessive dosages and its cumulative action the noxious effects of this drug should be realized and considerable care exercised in its use. Experimental investigators have shown that it is essentially a protoplasmic poison with an apparent selective action on muscle. The danger of administering the drug in excessive dosage or over prolonged periods is indicated by the pronounced degenerative changes produced in the cardiac musculature. Clinical manifestations of its toxicity consist of severe diarrhea, nausea and vomiting, profound prostration, cardiac arrhythmia and failure, muscular pains and weakness, especially in the extremities. The maximum amount of emetine that should be given over any period of time should not exceed 10 mg. (⅙ grain) of emetine hydrochloride per kilogram of body weight. Accordingly, for a patient weighing 150 pounds (about 68 Kg.) this would be about 0.65 Gm. (10 grains). Other amebicides, such as acetarsone, carbarsone, treparsol (the sodium salt of 3-formylamino-4-oxyphenylarsinic acid) chiniofon, vioform, and diodoquin (5,7-diiodo-8-hydroxyquinoline), which are safer and more efficient in the treatment of intestinal amebiasis, are not considered desirable in the treatment of amebic hepatitis and hepatic abscess because they are not as effective in these conditions as emetine and because they are toxic to the liver. However, immediately after completion of therapy of the hepatic condition the patient should be given a course of therapy for the intestinal amebiasis. While this frequently cannot be demonstrated clinically, it should be assumed to exist once the diagnosis of amebic hepatitis and hepatic abscess has been established. Moreover, the therapy employed for the latter should not be considered adequate for the treatment of the intestinal infestation. For this reason a separate and different type of therapy should be employed for the intestinal amebiasis.

Aspiration is the procedure of choice in cases in which evacuation of the abscess becomes necessary. In such cases, however, it should be realized that the preliminary administration of emetine is important. In the Tulane surgical service, emetine hydrochloride is administered routinely in daily doses of 0.065 Gm. (1 grain) for two or four days preceding the aspiration. Because the majority of amebic abscesses of the liver are sterile and because of the prognostic and therapeutic importance of this fact, every attempt should be made to maintain this sterility. The evacuation of such an abscess by open drainage is invariably followed by secondary infection, and the morbid consequences of this development have been previously emphasized. It is possible to evacuate the abscess and simultaneously maintain its sterility only by closed drainage. In the series of Ochsner and DeBakey open drainage was used in 80 cases, with a mortality of 22.1 per cent, and conservative therapy in 83, with 3 deaths, a mortality of only 3.6 per cent. Aspiration was performed without preliminary administration of emetine in 2 of these fatal cases, and within a relatively short period following the procedure manifestations of shock developed and the patients died. The other patient was treated with emetine and chiniofon by the medical service for almost three weeks, and no attempt was made to drain the hepatic abscess. At autopsy a huge hepatic abscess, measuring approximately 20 cm. in diameter, was found, in addition to several smaller abscesses. Ochsner and DeBakey expressed the firm conviction that these 3 tragedies could have been averted, the first 2 by preliminary administration of emetine and the third by aspiration of the abscess in addition to the use of emetine.

As previously emphasized, the procedure of aspiration should be performed in the operating room because the facility and reliability of strict asepsis are probably greater and because open drainage can be done immediately if the abscess is found to be secondarily infected. This may be determined readily by an immediate smear of the aspirated pus, which in cases of secondary infection would reveal on microscopic examination the presence of large numbers of bacteria

and leukocytes. The technic of aspiration has been described, and the procedure is performed in a similar manner for both diagnostic and therapeutic purposes. The administration of emetine should be continued after closed drainage of the abscess until 0.39 to 0.65 Gm. (6 to 10 grains) has been given. It is considered unnecessary as well as undesirable to introduce any substance into the abscess cavity, as the use of irrigating solutions of amebicides has been found to be valueless.

This last statement of Ochsner and DeBakey summarizes past experience in the treatment of amebic abscesses of the liver which have become secondarily infected. Recently Noth and Hirshfeld [56] reported the aspiration of such an amebic abscess that was infected with beta hemolytic streptococci of group G. They inserted a small ureteral catheter through the aspirating needle and used it to inject penicillin into the cavity of the abscess. Twenty-five thousand units of penicillin was injected every four hours for eight doses. The dose was then progressively decreased to 5,000 units every four hours. Injections of penicillin were maintained for fifteen and a half days, and a total of 830,000 units was administered. With this treatment the patient became afebrile and asymptomatic and recovery was uneventful.

HEPATIC DAMAGE FROM TANNIC ACID

One of the important medical problems of the war has been the treatment of burns. Several papers, including those of Wilson, Macgregor and Stewart [57] and McClure and Lam,[58] have called attention to the importance of hepatic necrosis in cases of severe burns. Jaundice is of bad prognostic omen in such cases. Wells, Humphrey and Coll [59] were the first to incriminate the then popular tannic acid therapy as the causative agent in the hepatic necrosis.

Patients treated with tannic acid had marked elevation of the icterus index, decreased plasma prothrombin and strongly positive reactions to cephalin flocculation tests. These tests of hepatic function elicited a normal response in patients treated with plain petrolatum.

Several investigators studied the problem experimentally. Forbes and Evans [60] showed that subcutaneous administration of tannic acid to rats resulted in hepatic necrosis. Cameron, Milton and Allen [61] found that tannic acid had an injurious effect on the livers of a variety of experimental animals and were able to demonstrate the absorption of tanic acid from burnt surfaces. Clark and Rossiter [62] showed that, in addition to the microscopic evidence of hepatic necrosis, functional impairment could be demonstrated by galactose tolerance tests. Additional detailed and confirmatory studies showing the poisonous effect of tannic acid on the liver and the changes in that organ after treatment of experimental burns with tannic acid have been reported by Hartman and Romence [63] and by Baker and Handler.[64]

The present consensus [65] is that the use of petrolatum or boric ointment gauze in the treatment of severe burns is preferable to application of tannic acid or other coagulation methods.

INDUSTRIAL POISONS AND DAMAGE TO THE LIVER

Numerous chemicals used in industry have a toxic effect on the liver. These have been discussed by Ottenberg and Spiegel. The exigencies of war cause a demand for numerous chemicals not commonly used in civilian industry.

Trinitrotoluene is one of the outstanding compounds in this class. During the last war it, together with the closely related nitrophenols (trinitrophenol [picric acid], etc.), was responsible for a great many cases of industrial poisoning and of toxic jaundice.[66] Evans [67] has

56. Noth, P. H., and Hirshfeld, J. W.: Amebic Abscess of the Liver with Secondary Infection: Local Treatment with Penicillin, J. A. M. A. **124**:643 (March 4) 1944.

57. Wilson, W. C.; Macgregor, A. R., and Stewart, C. P.: Clnical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, Brit. J. Surg. **25**:826 (April) 1938.

58. McClure, R. D., and Lam, C. R.: Problems in Treatment of Burns: Liver Necrosis as Lethal Factor, South. Surgeon **9**:223 (April) 1940.

59. Wells, D. B.; Humphrey, H. D., and Coll, J. J.: Relation of Tannic Acid to Liver Necrosis Occurring in Burns, New England J. Med. **226**:629 (April 16) 1942.

60. Forbes, J. C., and Evans, E. I.: Tannic Acid and Liver Necrosis, Surg., Gynec. & Obst. **76**:612 (May) 1943.

61. Cameron, G. R.; Milton, R. F., and Allen, J. W.: Toxicity of Tannic Acid: Experimental Investigation, Lancet **2**:179 (Aug. 14) 1943.

62. Barnes, J. M., and Rossiter, R. J.: Toxicity of Tannic Acid, Lancet **2**:218 (Aug. 21) 1943. Clark, E. J., and Rossiter, R. J.: Liver Function in Rabbits After Injection of Tannic Acid, ibid. **2**:222 (Aug. 21) 1943.

63. Hartman, F. W., and Romence, H. L.: Liver Necrosis in Burns, Ann. Surg. **118**:402 (Sept.) 1943.

64. Baker, R. D., and Handler, P.: Animal Experiments with Tannic Acid, Ann. Surg. **118**:417 (Sept.) 1943.

65. McClure, R. D.: Personal communication to the author.

66. Voegtlin, C.; Hooper, C. W., and Johnson, J. M.: Trinitrotoluene Poisoning: Its Nature, Diagnosis and Prevention, Hygienic Laboratory Bulletin 126, United States Treasury Department, Public Health Service,

(Footnotes continued on next page)

reported 7 cases of toxic necrosis of the liver with jaundice, with 2 fatalities, in British munition workers. Palmer, McShane and Lipman [68] reported 3 cases, with recovery in all. The jaundice came on suddenly and insidiously. Anorexia, nausea, vomiting and epigastric distress sometimes preceded the jaundice but sometimes appeared at the same time.

All the studies dealing with trinitrotoluene poisoning [69] have emphasized the importance of prevention of this disease by careful selection of workers and constant supervision of the conditions of their employment. The last include wearing of freshly laundered uniforms, an obligatory shower bath at the end of the work period, improved ventilation and use of respirators in some situations. Even with care there still may be excessive exposure to dust and fumes. The difference between the numbers of cases of poisoning reported at the present time and those reported during the past war is a measure of the value of these preventive measures.

Chlorinated hydrocarbons produced chemically by the chlorination of naphthalene and diphenyl and known by the trade name of Halowax are used extensively in the insulation of certain types of electrical cables. Workers handling Halowax acquired a characteristic type of dermatitis, which was described in Germany in 1927 [70] and by Schwartz [71] in this country.

Since the war a great deal of Halowax has been used in the manufacture of special electrical cables used on shipboard. Good and Pensky [72] have reviewed the extensive literature dealing with Halowax acne or "cable rash" that has appeared in consequence. The patients seen by Good and Pensky were exposed primarily to dust, and only a dermatitis developed. They encountered no cases of jaundice, and tests of hepatic function gave normal results. Schwartz [73] pointed out that jaundice and damage to the liver do occur among workers exposed to fumes of Halowax, but detailed reports are not yet available on cases of jaundice following poisoning by Halowax. I have encountered a number of such cases, and the clinical picture is that of an acute or subacute toxic jaundice, which may develop insidiously. Again the importance of preventive measures must be emphasized.

Tetrachlorethane is another toxic organic solvent which has been extensively used in industry during the war. Gurney [74] has described the medical measures taken in one plant to further the early recognition or prevention of poisoning and hepatic damage. Of a group of 277 employees, 75, or 27.1 per cent, had such symptoms or complaints as headache, giddiness, anorexia and nausea associated with exposure to the fumes of tetrachlorethane. Fifty-five, or 19.8 per cent, of these employees had enlargement of the liver. Only 6 had sufficient hepatic damage to produce clinical jaundice. Clinical recovery was prompt in all patients on removal from exposure to the gas and on standard treatment. Gurney stressed: (1) hygienic and preventive measures for reducing the exposure to toxic materials; (2) frequent physical examination, with emphasis on the size of the liver and clinical evidence of jaundice, and (3) widespread use of a few simple laboratory tests for hepatic injury. The laboratory tests were selected for their ease of application to large numbers of employees. That the tests took a minimum of the employees' time and required no special preparation and could be done with limited laboratory equipment were the chief factors in their selection. The tests used were those for bile and urobilinogen in the urine and determination of the icterus index and the cephalin flocculation test of the

1920. Discussion on the Origin, Symptoms, Pathology, Treatment and Prophylaxis of Toxic Jaundice Observed in Munition Workers, Proc. Roy. Soc. Med. **10**:106 (Jan.) 1917.

67. Evans, R. M.: T.N.T. Jaundice, Lancet **2**:552 (Nov. 8) 1941.

68. Palmer, W. L.; McShane, G. S., and Lipman, W. H.: Toxic Necrosis of the Liver from Trinitrotoluene: Report of Three Cases, J. A. M. A. **123**:1025 (Dec. 18) 1943.

69. Roberts, H. M.: The T.N.T. Health Hazard, Brit. M. J. **2**:647 (Nov. 8) 1941. Preventive Work in Connection with T.N.T. Poisoning, Bull. War. Med. **2**:526 (July) 1942. Discussion on Trinitrotoluene Poisoning, Proc. Roy. Soc. Med. **35**:553 (June) 1942. von Oettingen, W. F.: The Aromatic Amino and Nitro Compounds: Their Toxicity and Potential Dangers, Public Health Bulletin 271, Federal Security Agency, United States Public Health Service, 1941.

70. Teleky, L.: Die Pernakrankheit (Chloracne), Klin. Wchnschr. **6**:845 (April 30); 897 (May 7) 1927. Koelsch, F., in Ullmann, K.; Oppenheim, M., and Rille, J. H.: Die Schädigungen der Haut durch Beruf und gewerbliche Arbeit, Leipzig, Leopold Voss, 1926, pp. 303-343.

71. Schwartz, L.: Dermatitis from Synthetic Resins and Waxes, Am. J. Pub. Health **26**:586 (June) 1936; Skin Hazards in American Industry: Part II., Public Health Bulletin 229, United States Treasury Department, Public Health Service, 1936.

72. Good, C. K., and Pensky, N.: Halowax Acne ("Cable Rash"): A Cutaneous Eruption in Marine Electricians Due to Certain Chlorinated Naphthalenes and Diphenyls, Arch. Dermat. & Syph. **48**:247 (Sept.) 1943.

73. Schwartz, L.: An Outbreak of Halowax Acne ("Cable Rash") Among Electricians, J. A. M. A. **122**: 158 (May 15) 1943; footnote 71.

74. Gurney, R.: Tetrachlorethane Intoxication: Early Recognition of Liver Damage and Means of Prevention, Gastroenterology **1**:1112 (Dec.) 1943.

serum. My personal experience has confirmed the report of Gurney as to the usefulness of these tests in selecting patients for intensive study.

INTESTINAL OBSTRUCTION FROM GALLSTONES

Intestinal obstruction from gallstones has been the subject of comprehensive reviews by Foss and Summers [75] and Hinchey.[76] The spontaneous formation of a fistulous opening between the gallbladder and some portion of the intestinal canal is not an infrequent complication of cholecystitis, though statistical studies of its exact frequency are not available. When such an internal biliary fistula forms, any gallstones present in the gallbladder tend to be evacuated into the bowel. In 176 cases of cholecystoenteric fistula studied by Wakefield, Vickers and Walters [77] gallstones produced an intestinal obstruction in but 10. According to Foss and Summers,[75] this accident happened in only 0.3 per cent of the cases of disease of the gallbladder and bile ducts which had been observed by him. Other reports in the literature indicate that gallstones are responsible for from 1 to 6 per cent of cases of intestinal obstruction. Hand and Gilmore [78] collected reports of 12,153 cases of intestinal obstruction from the literature and found that gallstones were responsible for the obstruction in 208 cases, or 1.7 per cent.

Such cases are being recognized with increasing frequency, for von Wagner [79] in 1914 reported finding 334 cases in the literature. Moore [80] in 1925 reported 400 cases, while Foss and Summers [75] collected records of 140 other cases reported since then. The symptoms are variable. From 46 [75] to 50 [76] per cent of the patients give a history indicative of chronic disease of the gallbladder or suggestive of biliary colic. In 15 per cent of the cases reported by Foss the patients gave no history of previous ill health or indigestion. Approximately one third (32 per cent) give a history of an attack of epigastric pain sufficiently different from the previous biliary colic that it could be ascribed to perforation of the gallbladder or to passage of stones into the intestine.

Once in the intestine, small stones pass through the bowel and are evacuated without further incident. Stones large enough to produce ileus produce variable symptoms, depending on the site of the obstruction. Foss and Summers [75] reported that in 83 per cent of their cases with ileus the stone had lodged in the ileum and in 59 per cent it was in the terminal portion of the ileum, i. e., within 12 inches (30 cm.) of the ileocecal valve. According to Hinchey, 50 per cent of the patients give a recurrent history of obstructive symptoms, apparently associated with passage of the stone along the intestine.

The preoperative diagnosis is greatly facilitated by proper roentgenologic examination. Rigler, Borman and Noble [81] stressed the importance of (1) roentgenologic evidence of obstruction as demonstrated by scout films of the abdomen and (2) direct visualization of the stone, though, as Hinchey observed, it may be seen but is not always identified as a gallstone. If a Miller-Abbott tube has been passed successfully to deflate the obstructed bowel, the introduction of a small amount of thin barium sulfate solution may delineate the impacted stone. This is a safer diagnostic procedure than is the oral administration of barium sulfate. The demonstration of a cholecystoenteric fistula likewise is a valuable confirmatory sign in a case suspected to be one of intestinal obstruction due to gallstones. The biliary radicles may be outlined by gas in the ducts, or the fistula and biliary tree may be outlined by the regurgitation of barium sulfate from the intestinal canal.

Treatment is primarily surgical. Wangensteen [82] and Owens [83] reported cases in which decompression of the bowel with a Miller-Abbott tube relieved the symptoms of obstruction and the gallstone was passed by rectum shortly thereafter. This fortunate response is not the rule, for Hinchey and Hand reported cases in which the obstruction was not relieved by intubation.

Many of the patients are advanced in years, the average age in different series varying from 62 to 66. In a large proportion of cases either

75. Foss, H. L., and Summers, J. D.: Intestinal Obstruction from Gall Stones, Ann. Surg. **115**:721 (May) 1942.

76. Hinchey, P. R.: Gallstone Ileus, Arch. Surg. **46**:9 (Jan.) 1943.

77. Wakefield, E. G.; Vickers, P. M., and Walters, W.: Intestinal Obstruction Caused by Gallstones, Surgery **5**:670 (May) 1939.

78. Hand, B. H., and Gilmore, W. E.: Gallstone Ileus, Am. J. Surg. **59**:72 (Jan.) 1943.

79. Wagner, A.: Ileus durch Gallensteine, Deutsche Ztschr. f. Chir. **130**:353, 1914.

80. Moore, G. A.: Gallstone Ileus, Boston M. & S. J. **192**:1051 (May 28) 1925.

81. Rigler, L. G.; Borman, C. N., and Noble, J. F.: Gallstone Obstruction, J. A. M. A. **117**:1753 (Nov. 22) 1941.

82. Wangensteen, O. H.: The Therapeutic Problem in Bowel Obstruction: A Physiological and Clinical Consideration, Springfield, Ill., Charles C Thomas, Publisher, 1937.

83. Owens, F. M., Jr.: Gallstone Ileus: Successful Treatment with Miller-Abbott Tube, Gastroenterology **1**:938 (Oct.) 1943.

the diagnosis is not made or the decision to operate is reached only after a considerable delay. It therefore is not surprising that the operative mortality is about 50 per cent.

Early diagnosis and prompt surgical intervention give the greatest promise for a reduction in mortality. Search should always be made for further stones in the bowel, for numerous cases have been reported of recurrent obstruction from multiple gallstones in the intestine. It is still too soon to tell if the present vogue for the use of sulfanilamide crystals in the peritoneal cavity will reduce the operative mortality in cases of this type. Mastin [84] made the worth while suggestion that the risk of peritonitis from leakage of the suture line in the ileum may be obviated by delivering the loop of ileum containing the gallstone outside the abdomen and maintaining this exteriorization until the danger of leakage from the suture line is past.

The management of the biliary fistula should be regarded as a separate surgical problem from the relief of the intestinal obstruction. A cholecystocolic fistula is particularly likely to give rise to cholangitis, and its early closure is advocated.[77] When the biliary fistula is to the stomach, duodenum or jejunum, it is agreed that intervention frequently is unnecessary.

In the long run, earlier recognition of gallstones and removal of them before they have an opportunity to perforate into the intestine perhaps offer the greatest hope of reducing the danger of gallstone ileus.

84. Mastin, E. V., in discussion on Foss and Summers.[75]

Book Reviews

Gastro-Enterology. By Henry L. Bockus, M.D. Volume II. Price, 3 volumes and separate desk index, $35. Pp. 975, with 176 illustrations, 12 in colors. Philadelphia and London: W. B. Saunders Company, 1944.

This book is the second of a series of three volumes on gastroenterology prepared by a recognized authority in the field, who also is one of the outstanding teachers of modern medicine.

The volume begins with section IV of the series. The section is on diseases of the small intestine and consists of fifteen chapters. This section is followed by section V, on diseases of the colon, which consists of twenty chapters. The final section of the volume, section VI, deals with diseases of the peritoneum, mesentery and omentum and is divided into two chapters.

The section on the small intestine includes, in part, discussions of the clinical approach to the study of diseases of the mesenteric small intestine, embryology and anomalies, duodenal stasis, duodenitis, duodenal parasites, duodenal fistulas and other injuries, diverticulosis, tumors, regional enteritis, tuberculosis and idiopathic steatorrhea, and an excellent chapter on intestinal obstruction.

Under diseases of the colon, methods of study and examination based on the rich clinical experience of the author are outlined. The chapter on functional disorders of the colon is especially enlightening, and this difficult problem is dealt with in a sound and practical manner. The chapters on megacolon, melanosis and foreign bodies are instructive. The discussions of amebiasis and bacillary dysentery admirably set forth modern views and the best current treatment of these conditions. The book contains a long and detailed chapter on ulcerative colitis, in which the views of many contemporary workers are discussed. Perhaps too much space is devoted to the opinions of others in the discussion of causation of this group of infections. The reader would do well in reading this chapter to keep in mind that the discussion concerns itself with several disease entities, and to try to evaluate the author's views concerning them. The information gleaned in this way may be controversial, but it represents the latest published thought on the subject.

The first of the two chapters of section VI is concerned with the nature and structure of the peritoneum and with tumors and inflammations of the peritoneum and their treatment, as well as with evaluation of, and the technic of, peritoneoscopy. The second of the two chapters is concerned with the omentum and mesentery.

The entire volume offers highly instructive reading and leaves the reader with the thought that the task has been well done. It will serve as a useful reference volume for many years to come.

Osler's Principles and Practice of Medicine. Edited by Henry A. Christian, A.M., M.D., LL.D. (Hon.), Sc.D., Hon. F.R.C.P. (Can.), F.A.C.P. Fifteenth Edition. Price, $9.50. Pp. 1498. New York and London: A. Appleton-Century Company, Inc., 1944.

Only eighteen months after the fourteenth, or semicentennial, edition of this classic medical text, a fifteenth edition appears. This achievement is especially noteworthy when one considers the difficulty in obtaining material and labor during these war years and is first hand evidence of the demand of students and practitioners for the work.

This text by a single author is 1,498 pages in length, including a most detailed index, and adheres closely to the arrangement of the fourteenth edition. Scattered throughout the book one finds instances in which additions have been interpolated. For example, page 361 (1) deals with ornithosis, while page 361 (2) treats of phlebotomus fever. The indications for use of some of the newer drugs are mentioned in detail, as for example, penicillin and totaquine, and an up-to-date bibliography on these recent advances in medicine leaves little to be wished.

As a whole, the contents are so impressively handled that one is inclined to overlook the sketchy covering of some subjects, such as hemoglobinuria. The reviewer is impressed with the number of the rarer ills of man which the editor has contrived to include in this book.

The only real fault to be found is the manner of presenting the references. It would facilitate reading greatly to have them listed.

Plants and Vitamins. By W. H. Schopfer. Authorized translation by N. L. Noecker. Foreword by W. J. Robbins. Price, $4.75. Pp. XIV and 293. Waltham, Mass.: Chronica Botanica Company, 1943.

This book summarizes the present knowledge of vitamins in plants. The literature up to 1941 is reviewed fairly completely, and problems for future investigation are pointed out. As the author indicates, the volume shows only a stage of progress in research which continues to advance. Much of the material discussed is based on contributions of the author, who pioneered in this field and whose work has stimulated many subsequent investigations.

The book contains twenty-four chapters and is divided into three parts. Part I deals with the synthesis of vitamins in plants, auxoautotropic plants and research methods. In part II vitamins are discussed in relation to plants unable to synthesize them and considerable emphasis is given to growth factors of micro-organisms. Part III is concerned with general problems involving vitamins.

This book will be of interest primarily to animal and plant physiologists and to a lesser extent to others engaged in vitamin research, especially workers whose investigations involve bioassays with micro-organisms.

Allergy in Practice. By Samuel L. Feinberg. Price, $8. Pp. 798. Chicago: The Year Book Publishers, Inc., 1944.

In his introduction the writer states that he has tried to reach a middle ground between the elementary sketch of the subject and the "elaborate, unwieldy, cumbersome and often encyclopedic tome." At any rate he has produced an excellent book, clearly and concisely written and thoroughly documented with many references to the literature. The subject is covered, however, in the conventional manner, and, while the material is well up to date, there is nothing of startling novelty. The tables and illustrations are useful and the index is comprehensive.